Official Title:	**An Open-Label Study to Assess the Safety, Pharmacokinetics, and Pharmacodynamics of Treprostinil Palmitil Inhalation Powder in Participants with Pulmonary Arterial Hypertension**
NCT Number:	NCT04791514
Document Date:	Protocol Version 4: 03 June 2022 Protocol Version 3: 03 March 2022 Protocol Version 2: 06 October 2021 Protocol Version 1: 02 November 2020

APPENDIX 16.1 STUDY INFORMATION

16.1.1 Protocol and Amendments

Protocol/Amendment	Version	Date
Amendment 3	Version 4	03 June 2022
Amendment 2	Version 3	03 March 2022
Amendment 1	Version 2	06 October 2021
Protocol	Version 1	02 November 2020

Signature Page for INS1009-201 Protocol Amendment No. 3

Approve	[redacted] 03-Jun-2022 21:25:26 GMT+0000

CLINICAL STUDY PROTOCOL

An Open-Label Study to Assess the Safety, Pharmacokinetics, and Pharmacodynamics of Treprostinil Palmitil Inhalation Powder in Participants with Pulmonary Arterial Hypertension

Protocol Number: INS1009-201

Version Number: 4.0

Amendment Number: 3

Compound: Treprostinil Palmitil Inhalation Powder (TPIP)

Study Phase: 2a

Sponsor Name: Insmed Incorporated

Legal Registered Address:
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Bridgewater, NJ 08807-1704
USA

Regulatory Agency Identifier Number(s)
IND: 147264
EudraCT: 2022-000839-23
NCT: NCT04791514

Date: 03 JUN 2022

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ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ALT	alanine amino transferase
AST	aspartate amino transferase
AUC	area under the concentration-time curve
$AUC_{0-\infty}$	area under the concentration-time curve from time zero to infinity
AUC_{t1-t2}	area under the plasma concentration-time curve from time zero to time of last measurable concentration
CL/F	apparent total clearance of drug from plasma after extravascular administration
C_{max}	maximum (peak) plasma concentration of the drug
CO	cardiac output
CRF	case report form
CRO	contract research organization
CT	computerized tomography
DILI	drug induced liver injury
DPI	dry powder inhalation
ECG	electrocardiogram
EDC	electronic data capture
EOS	end of study
ERS/ERC	European Respiratory Society/European Society for Cardiology
EUT	extended use treatment
FDA	Food and Drug Administration

FVC	forced vital capacity
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
HL	Hy's Law
ICF	informed consent form
ICH	International Council for Harmonisation
ICU	intensive care unit
IMP	investigational medicinal product
IRB	investigational review board
IV	intravenous
MAD	multiple ascending dose
mPAP	mean pulmonary arterial pressure
MVO_2	mixed venous oxygen saturation
NO	nitric oxide
NOAEL	No observed adverse effect level
NT-pro-BNP	N-terminal (NT)-pro hormone brain natriuretic peptide
PAH	pulmonary arterial hypertension
PAP	pulmonary arterial pressure
PCWP	pulmonary capillary wedge pressure
PD	pharmacodynamic(s)
PH	pulmonary hypertension
PHL	potential Hy's Law
PI	principal investigator
PK	pharmacokinetic(s)

PVR	pulmonary vascular resistance
QD	once daily
QID	four times daily
RAP	right atrial pressure
RHC	right heart catheter
RVP	right ventricular pressure
SAD	single ascending dose
SAE	serious adverse event
SARS CoV 2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
SoA	schedule of activities/assessments
SUSAR	suspected unexpected serious adverse reaction
SRC	Safety Review Committee
$t_{1/2}$	elimination half-life
TBL	total bilirubin
TAPSE	tricuspid annular plane systolic excursion
TEAE	treatment emergent adverse event
t_{max}	time to maximum (peak) plasma concentration following drug administration
TPIP	treprostinil palmitil inhalation powder
TPIS	treprostinil palmitil inhalation suspension
TRE	treprostinil
TP	treprostinil palmitil
TVR	tricuspid valve regurgitation

ULN	upper limit of normal
US	United States
VCO_2	carbon dioxide production
Vd/F	apparent volume of distribution at terminal phase
WHO	World Health Organization
WOCBP	woman of child-bearing potential

1. PROTOCOL SUMMARY

1.1. Protocol Amendment Summary of Changes

Amendment 3 (03 JUN 2022)

This amendment is considered to be substantial.

Overall Rationale for the Amendment:

The primary driver for the changes in the protocol amendment is to better assure the potential for vascular reactivity of participants. To that end, there is the addition of a nitric oxide (NO) challenge, as well as refinement and clarification of inclusion/exclusion criteria.

Grammatical and typographical errors were corrected throughout the document.

A summary of major changes compared to the current global amendment is shown in the table below.

Revision	Rationale	Location of Revision
Updated the Schedule of Activities	To include an NO challenge, post-NO PD assessment, add assessments at 12 hours, and to clarify that PCWP is not only collected at Baseline (Table 2); To remove NT-pro-BNP and 6MWD test requirements for screening or baseline in the Extended Use Treatment Period (Table 5, Table 6); To clarify that historical values for NT-pro-BNP (or BNP) and 6MWD, within 3 months of first site visit or values at Baseline prior to RHC, are permitted; 6MWD is optional upon discussion with Medical Monitor (Table 2)	• Figure 1 • Table 1 • Table 2 • Table 5 • Table 6
Updated Inclusion Criterion #3	To include newly diagnosed participants	• Section 5.1
Updated Inclusion Criterion #4 (previously Inclusion Criterion #5)	To clarify requirement for stable therapy	• Section 5.1

Revision	Rationale	Location of Revision
Removed previous Inclusion Criterion #4	To remove functional class requirements	• Section 5.1
Removed previous Exclusion Criterion #18 and added guidance on concomitant therapy	To include washout guidance table and specify guidelines for handling CYP2C8 inhibitors	• Section 5.1 • Section 6.8.1
Updated Inclusion Criterion #2	To reduce redundancy with Inclusion Criterion #7	• Section 5.1
Removed previous Inclusion Criterion #6	To include participants with recent changes in diuretics	• Section 5.1
Updated Inclusion Criterion #5 (Previously Inclusion Criterion #7)	To adjust timing for documented predicted FVC requirement	• Section 5.1
Updated Inclusion Criterion #6 (Previously Inclusion Criterion #7)	To include Investigator assessment of low or intermediate risk participant	• Section 5.1
Removed previous Inclusion Criterion #10	To include participants with a wider range of BMI values	• Section 5.1
Clarified exploratory endpoint for 6MWD	Changed baseline from EUT baseline to study baseline	• Section 3.1
Clarified dosing that 112.5 µg dose will only be used in first participant	To clarify that only the first participant in the study will receive a dose containing 112.5 µg; subsequent participants will receive 80 µg, or a combination of capsules containing 80 µg, 160 µg, and 320 µg of TP, based on SRC recommendations.	• Section 1.3.2.1 • Figure 3 • Section 4.1 • Section 4.3.1 • Section 6.1.1 • Section 6.2
Added an exploratory endpoint	To evaluate the effect of NO challenge	• Section 3

Document History		
Document	**Version**	**Date**
Global Amendment 3	4.0	03 JUN 2022
Global Amendment 2	3.0	03 MAR 2022
Global Amendment 1	2.0	06 OCT 2021
Original Protocol	1.0	02 NOV 2020

1.2. Synopsis

Protocol Title:

An Open-Label Study to Assess the Safety, Pharmacokinetics, and Pharmacodynamics of Treprostinil Palmitil Inhalation Powder in Participants with Pulmonary Arterial Hypertension

Rationale:

Treprostinil palmitil (TP) is an inactive prodrug of treprostinil (TRE), which is widely used in the treatment of pulmonary hypertension (PH). Treprostinil palmitil inhalation powder (TPIP) is a dry powder for inhalation formulation of TP. TPIP is being developed for the treatment of pulmonary arterial hypertension (PAH; World Health Organization (WHO) Group 1 PH). TPIP is expected to provide extended release of TRE in the lung with the goals of less frequent and more convenient and consistent dosing while reducing the frequency and severity of dose-limiting side effects associated with the currently approved forms of TRE. No studies of TP or TPIP have been conducted in participants with PAH. The purpose of this study is to evaluate the safety, pharmacokinetics (PK), and pharmacodynamic (PD) effects of a single dose of TPIP in participants with PAH.

The starting and planned doses for this study are primarily based on the safety and tolerability of treprostinil palmitil inhalation suspension (TPIS) in healthy participants following single inhalation at 85 to 340 µg (Study INS1009-101) and TPIP in healthy participants in a SAD/MAD study (Study INS1009-102). In INS1009-101, the systemic exposure for TRE at 340 µg was low (AUC < 2.5 ng*h/mL) with an elimination $t_{1/2}$ of approximately 7 hours. In rats, the PK profile of TP inhalation solution was similar to that of TP inhalation powder. In INS1009-102, single doses of up to 675 µg and multiple doses of up to 225 µg for 7 days were administered to healthy participants. Overall, TP was well tolerated, with largely mild TEAEs and an adverse effect profile consistent with that of inhaled prostacyclin analogs. Treprostinil exposures increased approximately dose-proportionately, were similar between TPIS and TPIP, and showed no accumulation with once daily (QD) dosing.

Objectives and Endpoints:

Objectives	Endpoints
Primary	Primary
• To evaluate the safety and tolerability of single doses of TPIP in participants with PAH	• Frequency of TEAEs
Secondary	Secondary
• To evaluate the PD effects of single doses of TPIP on PVR in participants with PAH over the first 24 hours following administration	• Change from Baseline in PVR at 8 and 24 hours after TPIP administration
• To evaluate the PK of TPIP as TRE in participants with PAH	• C_{max}, t_{max}, $AUC_{t1–t2}$, $AUC_{0–\infty}$, $t_{1/2}$ of TRE in plasma

TPIP=treprostinil palmitil inhalation powder; PAH=pulmonary arterial hypertension; TEAE=treatment emergent adverse event; PD=pharmacodynamic; PVR=pulmonary vascular resistance; PK=pharmacokinetics; TP=treprostinil palmitil; TRE=treprostinil; C_{max}=maximum observed concentration; t_{max}=time to maximum concentration after drug administration; $AUC_{t1–t2}$= area under the concentration time curve from time zero to last sampling time point with measurable concentration; $AUC_{0–\infty}$=area under the concentration time curve from time zero to infinity; $t_{1/2}$=elimination half-life

Overall Design:

This is a Phase 2a open-label study to assess the safety, tolerability, PD effects, and PK of TPIP administered to participants with PAH. This is the first study of TPIP in participants with PAH. Each participant will receive a single dose of TPIP, which may vary from participant to participant, as determined by the Safety Review Committee (SRC) for the study. The first participant in the study will receive a dose containing 112.5 µg; subsequent participants will receive 80 µg, or a combination of capsules containing 80 µg, 160 µg, and 320 µg of TP, based on SRC recommendations. The study includes a 24-hour inpatient observation period following TPIP dosing, during which PK, PD, and safety parameters will be assessed. An optional extended treatment period of 16 weeks will be available to participants who have completed the single-dose inpatient treatment period. When available, participants may be eligible to enroll in a separate open-label extension study (OLE) study that will have a duration of approximately 2 years. Details of the planned OLE study will be provided in a separate protocol. The study is designed to ensure the safety of and maintain minimal risk to participants. The cardiopulmonary and overall functional status of participants with PAH can be labile and medical instability can develop quickly. As such, there is considerable flexibility built into the protocol to allow Investigator discretion with the frequency, timing, and/or conduct of PD and PK assessments to again ensure participants' safety.

Brief Summary:

The study is designed to investigate the safety and acute pharmacokinetic (PK) and pharmacodynamic (PD) effects of a single dose of treprostinil palmitil inhalation powder (TPIP) in participants with pulmonary arterial hypertension (PAH). Intensive monitoring of pulmonary vascular resistance, cardiac output, right ventricular pressure, pulmonary arterial pressure, hemoglobin, right atrial pressure, and mixed venous oxygen saturation via right heart catheter in an appropriate inpatient setting is essential to understand how TPIP affects cardiopulmonary hemodynamics and to elucidate dose- and PK-effect relationships. Some assessments and study activities (resting respiratory gas exchange assessment, transthoracic echocardiogram, pulmonary computerized tomography scan) for exploratory endpoints are optionally left to the discretion of the individual Investigator, based on participant safety and study site capabilities.

For individual participants, the study will consist of an outpatient screening period lasting up to 30 days. The inpatient treatment period will start on Study Day 1 and is expected to last overnight into Study Day 2. Outpatient PK sampling and safety follow-up at 48 hours post TPIP dose will extend into Study Day 3. A remote safety follow-up visit (telephone visit) is scheduled for Study Day 30 (± 2 days). An optional extended treatment period of 16 weeks will be available to participants who have completed the single-dose inpatient treatment period. There will be a second safety follow-up visit 30 days (± 3 days) after extended use treatment (EUT) Week 16 for participants who elect to enter the extended use treatment period. If the initial remote safety follow-up visit overlaps with the start of the extended treatment period, the initial remote safety visit will be shortened and conducted just prior to administration of IMP in the extended treatment period.

Number of Participants:

Approximately 6 to 10 evaluable participants are planned. Evaluable participants for safety are those who receive a single dose of TPIP; evaluable participants for PD and PK endpoints are those who receive a single dose of TPIP and have at least 1 post-TPIP administration PK or PD datapoint.

Treatment Groups and Duration:

This is a multi-center, open-label, non-randomized study. There are no predefined treatment groups. The dose determination for each participant will be made based on all available PK, PD, and safety data at the time of the participant's entry into the study. An optional extended use treatment period of 16 weeks will be available to all participants.

Safety Review Committee:

A Safety Review Committee (SRC) will be responsible for monitoring safety data. The SRC will comprise all Investigators and key members of the Insmed Study Team (including but not limited to Medical Monitor, Medical Director(s), Safety/Pharmacovigilance Physician, Statistician, Clinical Pharmacologist) and external expert consultants. The SRC will continuously monitor all available safety, PD and PK data for each participant and will obtain consensus regarding the safety of continuing the study, the next TPIP dose, and clinical care of the next participant. Expert consultants may be invited to review and interpret participant data. With any safety findings, a decision will be made, based on the review, as to whether enrollment in the study will

be allowed to continue. Decisions regarding final database values for PD parameters may be adjudicated by the SRC.

1.3. Schema

1.3.1. Participant Progression Through the Study

The main study comprises an outpatient screening period, an inpatient treatment period, and an outpatient follow-up period. Participant progression through the study is shown in Figure 1. An optional EUT period is shown in Figure 2.

1.3.1.1. Screening Period

The outpatient screening period will last up to 30 days. After participants complete screening and have met the study eligibility criteria, the right heart catheter (RHC) procedure and inpatient treatment period should be scheduled without delay.

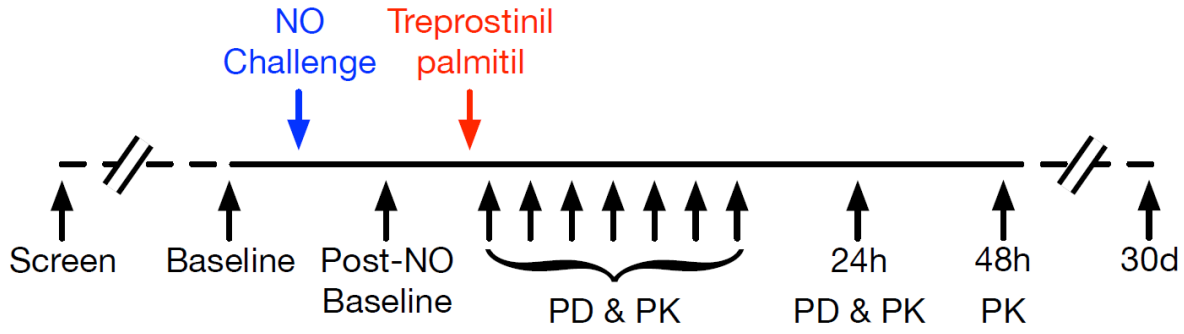
1.3.1.2. Inpatient Treatment Period

The inpatient treatment period will start on Study Day 1 and extend overnight into Study Day 2. Because the study requires an inpatient treatment period, institutional requirements for elective inpatient admissions, which may vary from site to site, will be followed. The participant may be required to undergo pre-admission assessments required by the institution for elective admission, for example testing for common infectious pathogens. Signature of elective admission documents and other consents may be required by the institution. An RHC will be placed. Following completion of Baseline assessments, a single dose of TPIP will be administered via a dry powder inhaler. Safety, PD, and PK assessments will continue at scheduled intervals through 24 hours following TPIP administration. Following the final assessments at 24 hours, the RHC will be removed and the participant will be discharged from the inpatient setting when deemed safe for the participant.

1.3.1.3. Follow-up Period

PK blood draw at 48 (± 4) hours after TPIP dosing will be done on an outpatient basis as arranged by the site. The 48-hour post-TPIP visit will also include safety assessments including physical examination, clinical laboratory evaluations, ECG, AE collection and vital signs. An additional safety follow-up will be conducted by telephone call or telemedicine on Study Day 30 (± 2 days) unless the participant elects to enter the EUT period prior to this follow-up visit. If the initial remote safety follow-up visit overlaps with the start of the extended treatment period, the initial remote safety visit will be shortened and conducted just prior to administration of investigational medicinal product (IMP) in the extended treatment period.

Figure 1: Participant Progression Through INS1009-201 Study[a]



NO=nitric oxide; PD-pharmacodynamic assessments; PK=pharmacokinetic assessments; h=hours; d=days
[a] Does not include optional extended use treatment period; the 30 day follow-up visit will be shortened and conducted just prior to administration of IMP in the extended treatment period if the visit overlaps with the start of the extended treatment period.

1.3.1.4. Optional Extended Use Treatment Period

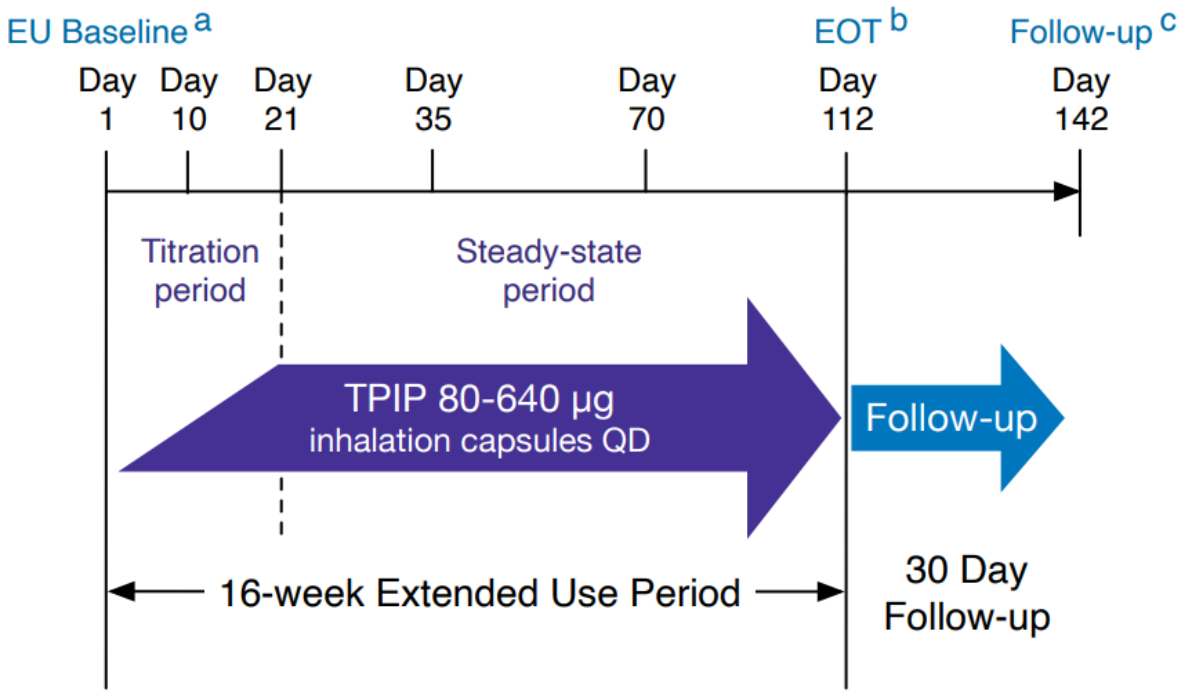
All participants will be allowed to enter the optional 16 week EUT period after the completion of the inpatient treatment period and final PK sample collection. Entry into the optional EUT period will be at participant and Investigator discretion. A gap between the inpatient treatment period and EUT period is expected, but not required, and can be up to 6 months.

After collection of the final PK sample, all participants will be allowed optional continued access to IMP for 16 weeks (includes a 3-week titration period) from first administration in the EUT period. At the Investigator's discretion, participants may undergo a study drug taper for up to 2 weeks after the Week 16 visit to help facilitate a safe withdrawal from study drug.

Participants will be screened to ensure they meet inclusion and exclusion criteria if they enter the EUT period more than 30 days after beginning the single-dose period (e.g., beyond the initial 30 day follow-up period) (Table 5).

Participant in-clinic study visits will be scheduled for EUT at Baseline (EUT Day 1), EUT Week 2, EUT Week 3, EUT Week 5, EUT Week 10, and EUT Week 16.

Figure 2: Participant Progression Through the Optional Extended Use Treatment Period



[a] The 30 day follow-up visit from the single dose period will occur on EU Day 1 if the visit overlaps with the start of the extended treatment period.
[b] At the Investigator's discretion, participants may undergo a study drug taper for up to 2 weeks after the Week 16 visit.
[c] The follow-up telephone call or visit will be 30 days after the Week 16 visit.
EU = Extended Use; QD = once daily; EOT = end of treatment

1.3.1.5. Extended Use Follow-up Period

There will be a second remote safety follow-up visit 30 days (± 3 days) after EUT Week 16 administration for participants who elect to enter the EUT period.

1.3.2. Dose Selection

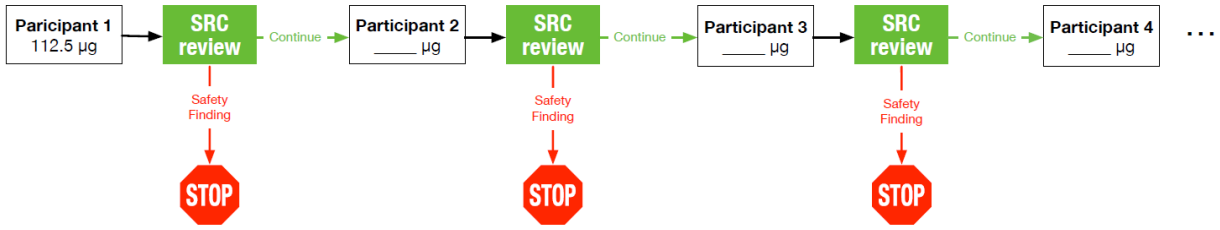
1.3.2.1. Inpatient Treatment Period Dose Selection

Each participant will enter the study in a serial fashion, following review of available safety, PK, and PD data from all previous participants by the Safety Review Committee (SRC). Each participant will receive a single-dose administration of TPIP via a dry powder inhaler. TPIP will be administered to only one participant at a time, with full evaluation of all available data prior to dosing the next participant.

The first participant will receive a dose of TPIP containing 112.5 µg. Subsequent participants will receive 80 µg, or a combination of capsules containing 80 µg, 160 µg, and 320 µg of TP,

based on SRC recommendations. After the first participant, the SRC will review all available safety, PD, and PK data including data from the first participant and select the TPIP dose and any changes to the assessments for the second participant. Then, following review of all available data including that from the first and second participants, the SRC will select the dose for the third participant. Similarly, all available data from previous studies and participants will be assessed prior to determining the dose for the next participant, until such a time as the SRC believes the study must conclude. Figure 3 describes the planned dose-selection and study continuation process.

Figure 3: Schematic of Study Continuation Planning after Participant 1, INS1009-201



SRC=Safety Review Committee

1.3.2.2. Optional Extended Use Treatment Period

Entrance into the optional EUT period is at participants' and Investigators' discretion and begins with a titration. The guideline for the optimal 3-week planned titration schedule is provided in Figure 4. The target TPIP dose will be achieved with a combination of dry powder capsules containing 80 µg, 160 µg, and 320 µg of TP.

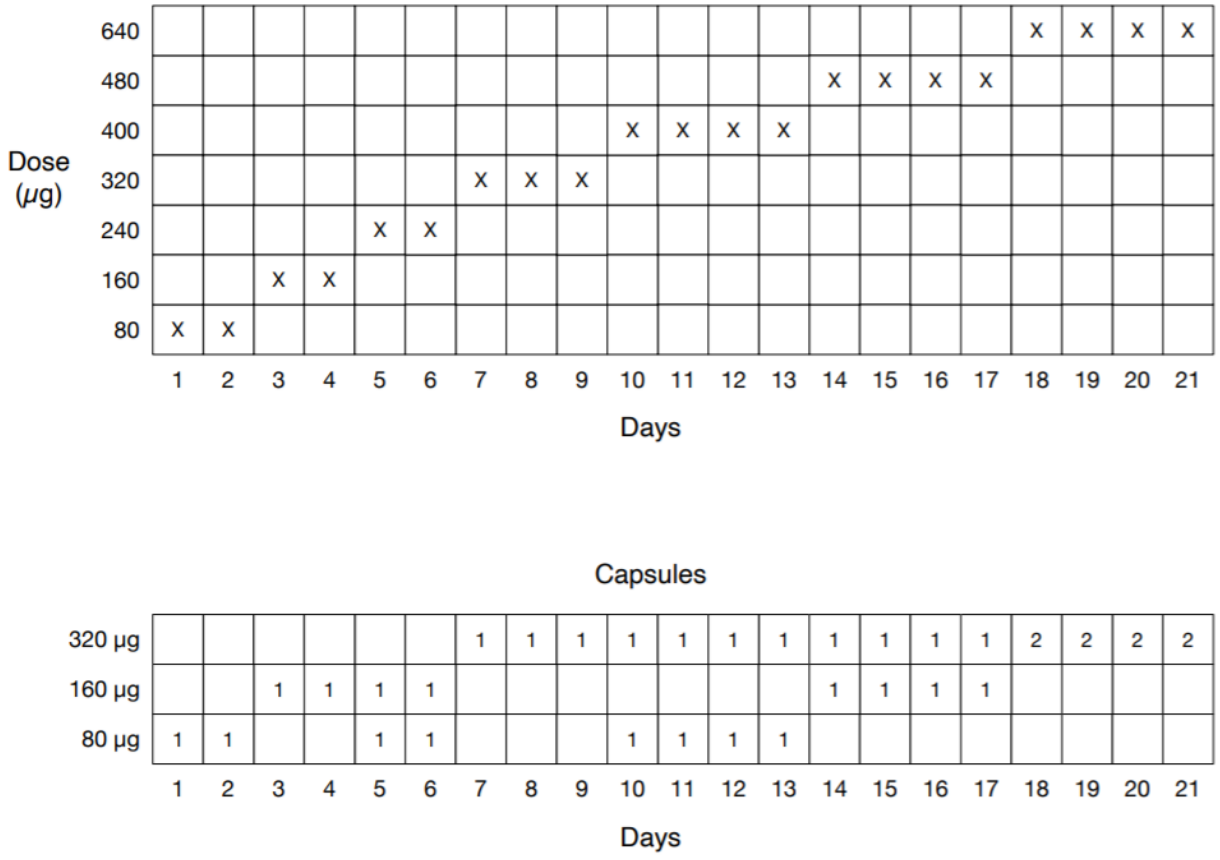
During the titration period (EUT Days 1 to 21), each participant's dose will be up-titrated to the highest tolerated dose for that individual. Participants will start open-label study drug with 1 capsule (80 µg TPIP) QD. If this dose is well tolerated, the dose should be up-titrated until reaching the participant's highest tolerable dose as described by the dosing schedule in Figure 4. During this titration period, participants must stay on study drug for the minimum number of cumulative days required for each dose (e.g., 2 days at 80 µg, 160 µg, or 240 µg; 3 days at 320 µg; or 4 days at 400 µg or 480 µg) prior to titrating to the next higher dose. Study drug titration may occur slower, but not faster, than described in Figure 4. If a dose is not tolerated, study drug may be decreased to the previous dose level. At the Investigator's discretion, up-titration may resume (as described in Figure 4) until the participant's highest tolerated dose is achieved at EUT Day 21.

All dose adjustments must be preceded by contact with the Investigator or study site personnel. In addition, the Investigator and/or study site personnel will be in contact with participants during the dose adjustment period to assess the tolerability to study drug as measured by the AEs commonly observed with other prostacyclin receptor agonists, which include headache, flushing, nausea, cough, and muscle pain. The decision to up-titrate to the next TPIP dose will be based on safety and tolerance data (e.g., AEs) as reported by the participant and assessed by the Investigator.

At the Investigator's discretion, based on tolerability, the study drug dose may be increased by 1 dose level (as described in Figure 4) at the EUT Week 5 in-clinic visit for participants who have not achieved the 640 µg dose. The increase in dose will be administered under clinical observation at the study site to ensure tolerability and correct dosing and self-administration of study drug. The participant's highest dose tolerated is expected to continue for the remainder of the study after the EUT Week 5 visit.

At the Investigator's discretion, participants may undergo a study drug taper for up to 2 weeks after the EUT Week 16 visit to help facilitate a safe withdrawal from study drug. The Investigator and/or study site personnel will be in contact with participants during the study drug taper to assess the tolerability to study drug.

Figure 4: Guideline for Optimal 3-Week Planned Titration Schedule (Optional Extended Use Treatment Period)



1.4. Schedule of Activities (SoA)

The SoA is divided into the following tables:

- Screening and follow-up activities in the single-dose period
- SoA in the inpatient treatment period

- PK and PD biomarker blood sampling schedule
- Optional procedures and assessments in the inpatient treatment period
- Screening and follow-up activities in the EUT period
- SoA in the EUT period

The single-dose period refers to the combination of the inpatient treatment period (Study Day 1 to Study Day 2), the PK/PD sampling period, and the 30 day follow-up period.

Table 1: Schedule of Activities for Screening and Follow up, Single-Dose Period, INS1009-201

Procedure	**Screening**	**Follow-up**	
	Up to 30 Days	**48 h post TPIP dose**[a]	**Study Day 30 (± 2 days)**[b]
Informed Consent	X	--	--
Inclusion/Exclusion Criteria	X	--	--
Demographics and Medical History	X	--	--
Smoking Status	X	--	--
Height, Weight	X	--	--
Prior/Concomitant Medications	X	X	X
Serology (HBsAg, HIV antibody, HCV antibody)	X	--	--
Serum Pregnancy Test (WOCBP only)	X	—	—
Urine Pregnancy Test (WOCBP only)	--	—	X
Hematology, Clinical Chemistry (Table 8)	X	X	--
Coagulation Profile (Table 8)	X	--	--
12-lead ECG	X	X	--
Physical Examination	X	X	--
Vital Signs	X	X	--
Pulmonary Function Testing (if needed, (Section 5.1)	X	--	--
Adverse Events[c]	X	X	X

[a] 48 h safety follow-up assessments are to be conducted at the time of the visit for the 48h PK blood draw (Table 3).
[b] Follow-up visit will be shortened and conducted just prior to administration of IMP in the extended treatment period if the visit overlaps with the start of the extended treatment period.

[c] AE collection is from the time of signing the informed consent through the Day 30 safety follow-up. Events between ICF signing and TPIP dosing that are serious will be recorded as SAE; non-serious events during this period must be recorded as medical history.

BMI = body mass index; ECG = electrocardiogram WOCBP = woman of childbearing potential

Note: Additional safety follow-ups may be conducted at any time per the investigator's discretion to ensure participant safety. The reason for any additional safety follow-up must be reported as an AE.

Table 2: Schedule of Activities for Inpatient Treatment Period, INS1009-201

	Treatment Period (Study Day 1 to Study Day 2)													
	Pre-TPIP Administration			**TPIP Administration**	**Post-TPIP Administration**									
Procedure	Day 1 Baseline	NO value[a]	Post-NO Baseline[a]	Time 0	30 min	60 min	90 min	2 h	3 h	4 h	8 h	12 h	24 h	24 h to discharge
Hematology, clinical chemistry, coagulation profile blood draw[b]	X	--	--	--	--	--	--	--	--	--	--	--	X	--
Urine pregnancy test (WOCBP only)	X	--	--	--	--	--	--	--	--	--	--	--	--	--
12-lead ECG	X	--	--	--	--	--	--	--	--	--	--	--	--	--
Cardiac telemetry per institutional protocol[c]	X	←	―	―	―	―	―	―	―	―	―	―	―	→
Physical Exam	X	--	--	--	--	--	--	--	--	--	--	--	--	X
Vital signs[d]	X	--	--		X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	←	―	―	―	―	―	―	―	―	―	―	―	→
Adverse events collection	X	←	―	―	―	―	―	―	―	―	―	―	―	→
Place right heart catheter	X	--	--	--	--	--	--	--	--	--	--	--	--	--
NT-pro-BNP or BNP[e]	X	--	--											
6MWD[e]	X	--	--											
PD assessments: PVR, MVO_2, Hgb, RVP, PAP CO, PVR, RAP, oxygen consumption, PCWP, heart rate, SpO_2, systemic blood pressure[f]	X	--	X	--	X	X	X	X	X	--	X	X	X	--
NO Challenge	--	X	--	--	--	--	--	--	--	--	--	--	--	--

	Treatment Period (Study Day 1 to Study Day 2)													
	Pre-TPIP Administration			**TPIP Administration**	**Post-TPIP Administration**									
Procedure	Day 1 Baseline	NO value	Post-NO Baseline	Time 0	30 min	60 min	90 min	2 h	3 h	4 h	8 h	12 h	24 h	24 h to discharge
Administer TPIP	--	--	--	X	--	--	--	--	--	--	--	--	--	--
Remove RHC	--	--	--	--	--	--	--	--	--	--	--	--	--	X
Discharge/Safety Follow-up Instructions	--	--	--	--	--	--	--	--	--	--	--	--	--	X

[a] Exception to NO challenge and post-NO Baseline assessment is allowed for sites without the technical ability/equipment to effectively carry out the assessment, as determined by the Sponsor.
[b] See Section 10.2, Table 8 for specific laboratory tests.
[c] Routine cardiac telemetry readings will not be collected as study data unless they pertain to a relevant adverse event.
[d] Heart rate, systemic blood pressure, and SpO_2 are required PD measurements and will be collected as scheduled. They may be measured with pulse oximetry for heart rate and SpO_2 and an automated inflatable arm cuff for blood pressure. Temperature and respiratory rate may be measured per institutional inpatient protocol. Respiratory rate will be measured as part of pulmonary gas exchange testing, if performed.
[e] Historical values for Baseline NT-pro-BNP and 6MWD are permitted up to 3 months before Baseline visit. If the tests are performed at the Baseline visit, they must be performed prior to RHC. The 6MWD test is optional if discussed with the Medical Monitor.
[f] Systemic blood pressure must include 3 values: systolic, diastolic, and mean arterial pressure.
CO = cardiac output; Hgb = hemoglobin; MVO_2 = mixed venous oxygen saturation; NO = nitric oxide; PAP = pulmonary arterial pressure; PVR=pulmonary vascular resistance; RAP = right atrial pressure; RVP = right ventricular pressure; SpO_2 = arterial blood oxygen saturation; WOCBP = woman of childbearing potential

Table 3: PK and PD Biomarker Sampling Schedule, Single-Dose Period, INS1009-201

--	**Baseline Pre-TPIP Administration**	**TPIP administration**	**Post-TPIP Administration**						
Time	--	0	30 (± 10) mins	60 (± 10) mins	2 h (± 20) mins	4 (± 1) h	8 (± 2) h	24 (± 2) h	48 (± 4) h
PK sampling[a]	X	--	X	X	X	X	X	X	X
Biomarker sampling[b]	X	--	--	--	--	X	X	--	--

[a] PK sampling for treprostinil palmitil and treprostinil; each PK sample will be approximately 10 mL.
[b] Each biomarker sample will be approximately 5 to 7 mL.

Table 4: Schedule for Optional Procedures and Assessments, Inpatient Treatment Period, INS1009-201

Inpatient Treatment Period (Study Day 1 to Study Day 2)										
	Pre-TPIP Administration	**TPIP Administration**	**Post-TPIP Administration**							
Procedure	Study Day 1 Baseline	Time 0	2-8 hr	4-8 hr						
Transthoracic echocardiogram (LVEF,TVR maximum velocity, TAPSE, end diastolic right ventricular volume)	X	--	X	--						
Pulmonary CT scan (total blood volume, blood volume in vessels < 5 mm^2)	X	--	--	X						
--	**Pre-TPIP Administration**	**TPIP Administration**	--							
--	Study Day 1 Baseline	Time 0	30 mins	60 mins	90 mins	2 h	3 h	4 h	8 h	24 h
Resting respiratory gas exchange assessment[a] (respiratory rate, minute ventilation, VCO_2, ETO_2, $ETCO_2$, SpO_2	X	--	X	X	X	X	X	--	X	X

[a] Resting respiratory gas assessment parameters are collected at the same time points as RHC parameters with the exception of the 12 h timepoint.

NOTE: Parameters to be measured for each procedure are in parentheses.

CT=computerized tomography; $ETCO_2$ =end tidal carbon dioxide concentration; ETO_2,=end tidal oxygen concentration; LVEF=left ventricular ejection fraction; SpO_2=arterial blood oxygen saturation; TAPSE=tricuspid annular plane systolic excursion; TVR=tricuspid valve regurgitation; VCO_2,=carbon dioxide production

Table 5: Schedule of Activities for Screening and Follow-up, Extended Use Treatment Period, INS1009-201

Procedure	Screening[a]	Follow-up
	EUT Study Day 1 (± 3 days)	EUT Study Day 142 (± 3 days)
Informed Consent	X	--
Inclusion/Exclusion Criteria	X	--
Demographics	X	--
Smoking Status	X	--
Height, Weight	X	--
Prior/Concomitant Medications	X	X
Urine Pregnancy Test (WOCBP only)	X	X
Hematology, Clinical Chemistry (Table 8)	X	--
12-lead ECG	X	--
Vital Signs	X	--
Adverse Events[b]	X	X

[a] Participants will only be screened at EUT Day 1 if they enter the EUT period beyond 30 days after beginning the single-dose period (e.g., beyond the initial 30 day follow-up period).
[b] AEs for the period from the Study Day 30 follow-up until the enrollment in the EUT period will be collected during participants' screening for the EUT.
BMI = Body Mass Index; EUT = extended use treatment; WOCBP = woman of childbearing potential

Table 6: Schedule of Activities for the Optional Extended Use Treatment Period, INS1009-201

Period	Extended Use Treatment Period						Follow-Up	E/D[a]
Week	EUT W1	EUT W2	EUT W3	EUT W5	EUT W10	EUT W16	EUT W20[b]	
Day	EUT D1 (Screening[c] and Baseline)	EUT D10 (± 3 days)	EUT D21 (± 3 days)	EUT D35[d] (± 3 days)	EUT D70 (± 3 days)	EUT D112 (± 3 days)	EUT D142 (± 3 days)	
Visit	EUT V1	EUT V2	EUT V3	EUT V4	EUT V5	EUT V6	EUT V7	
Inclusion/exclusion	X[c]	--	--	--	--	--	--	--
Prior/concomitant medications	→							
Pregnancy test (WOCBP only)[e]	X[c]	→						X
Vital signs[f]	X	X	X	X	X	X	--	X
6MWD test	--	--	--	--	--	X	--	--
Hematology, clinical chemistry [g]	X[c]	--	--	--	--	--	--	--
12-lead ECG	X[c]	--	--	--	--	--	--	--
NT-pro-BNP (or BNP) Sample	--	--	--	--	--	X	--	--
Optional pulmonary CT scan (total blood volume, blood volume in vessels < 5 mm^2)	X	--	--	--	--	X	--	--
Study drug distribution[h]	X	X	X	X	X	X	--	--
Study drug self-administration re-assessment[i]	--	X	X	X	X	X	--	--
Targeted physical examination[j]	X	--	X	X	X	--	--	--
Study drug accountability[k]	--	X	X	X	X	X	X[l]	--

Period	Extended Use Treatment Period						Follow-Up	E/D[a]
Week	EUT W1	EUT W2	EUT W3	EUT W5	EUT W10	EUT W16	EUT W20[b]	
Day	EUT D1 (Screening[c] and Baseline)	EUT D10 (± 3 days)	EUT D21 (± 3 days)	EUT D35[d] (± 3 days)	EUT D70 (± 3 days)	EUT D112 (± 3 days)	EUT D142 (± 3 days)	
Visit	EUT V1	EUT V2	EUT V3	EUT V4	EUT V5	EUT V6	EUT V7	
Dosing diary	→						--	--
Adverse events[m]	→							

[a] Participants who enroll in the optional EUT period and discontinue before the end of study will be classified as early discontinuations.
[b] Follow-up telephone call or visit will be 30 days after the EUT Week 16 visit.
[c] Participants will undergo assessments for screening at EUT Day 1 if they enter the EUT period beyond 30 days after beginning the single dose period (e.g., beyond the initial 30 day follow-up period).
[d] At the Investigator's discretion, an increase of 1 dose level may be allowed at EUT Week 5 if the participant has not achieved the 640 µg dose.
[e] Pregnancy test: Urine pregnancy tests will be performed in-clinic at EUT Baseline (EUT Day 1) in WOCBP. WOCBP will be provided home pregnancy test kits with instructions to conduct the pregnancy tests every 30 days or more if required during the treatment and follow-up periods. Study site personnel will contact the participant every 30 days by telephone and record the pregnancy test results. An additional on-site urine test must be performed prior to starting any procedure that requires the use of ionizing radiation.
[f] Vital signs: Includes body temperature (°C), pulse rate (bpm), respiratory rate (breaths/min), blood pressure (systolic, diastolic, and mean arterial [mmHg]), and SpO_2. Vital signs will be measured at EUT Screening/Baseline (EUT Day 1), EUT Week 2, EUT Week 3, EUT Week 5, EUT Week 10, and EUT Week 16 and at the Early Discontinuation visit, if appropriate.
[g] See Table 8 for additional information.
[h] Participants will receive study drug supply on EUT Day 1 and at EUT Week 2, EUT Week 3, EUT Week 5, and EUT Week 10 visits. Participants who undergo a study drug taper will receive study drug supply at the EUT Week 16 visit. A telephone call from study personnel or the Investigator will be placed to participants assigned to a study drug taper to check on the participant's well-being; timing of the telephone call will be based on the Investigator's discretion, and any adverse events will be captured on the CRF.
[i] Assessment of study drug self-administration: Study drug self-administration will be overseen by study site personnel at all in-clinic visits.
[j] The targeted physical examination will be performed at Week 3, Week 5, and Week 10 prior to study drug administration. The targeted physical exam includes cardiovascular (cardiac auscultation, assessment of peripheral pulses and edema) and pulmonary assessments (pulmonary auscultation).
[k] Participants will return unused capsules and used capsules and devices to the study site at the Week 2, Week 3, Week 5, Week 10, and Week 16 visits.
[l] Participants who undergo a study drug taper will return unused capsules and used capsules and devices to the study site at a follow-up visit.
[m] AE collection from the 30 day follow-up period in the single-dose period to enrollment in the EUT period will be queried during EUT screening; All other AEs and SAEs will be collected from EUT Day 1 and followed up as described in Section 8.3.3.
6MWD = 6-minute walk distance; CT = computerized tomography; CRF = case report form; D = day; E/D = early discontinuation; EUT = extended use treatment; NT-pro-BNP = N-terminal pro B-type natriuretic peptide; W = week; WOCBP = woman of childbearing potential; V = Visit

2. INTRODUCTION

Pulmonary hypertension (PH), a hemodynamic state characterized by resting mean PAP > 20 mmHg per updated guidelines (Simonneau et al., 2019), is generally classified into 5 groups based on the underlying pathology: Group 1 is PH due to pulmonary vascular disease, also known as pulmonary arterial hypertension (PAH); Group 2 is PH due to left heart disease; Group 3 is PH due to lung disease or hypoxia; Group 4 is PH due to chronic thromboembolic disease or other pulmonary vasculature obstruction; Group 5 is miscellaneous PH syndromes caused by a variety of disorders such as hemolytic anemias and sarcoidosis (Thenappan et al., 2018).

In Group 1 PH (PAH), the resting mean PAP > 20 mmHg occurs in the setting of normal pulmonary arterial wedge pressure of ≤15 mm Hg with PVR of ≥3 Wood Units (WU) (McLaughlin et al., 2009). In PAH the pulmonary vasculature is affected by vasoconstriction, vascular remodeling, increased rigidity of vessel walls and vascular fibrosis. These vascular anomalies increase PVR, which leads to increases in right ventricular afterload, and a cascade of maladaptive changes to the heart including right ventricular hypertrophy, ischemia and fibrosis, reducing right ventricular function and eventually leading to right ventricular failure and death (Thenappan et al., 2018). The pulmonary vascular lesions of PAH may be idiopathic, hereditary, or occur as a complication of drug use (e.g., anorexigens), connective tissue disease, portal hypertension, congenital cardiac malformations or HIV infection (Hoeper et al., 2017).

Data from PAH registries around the world (Thenappan et al., 2018) estimate a global incidence ranging from 2.0 to 7.6 cases per million adults per year, with a prevalence of 11 to 26 cases per million adults; the incidence in females is approximately 4 times that in males. Most registries report a mean age of onset ranging from approximately 36 to 53 years. While overall median survival has improved from 2.8 years in the 1980's to 6 years currently, mortality is high, with 1 year survival ranging from 68% to 93% and 5 year survival ranging from 21% to 65%. Nearly half of the patients in these registries have PAH of idiopathic, heritable or anorexigen-induced origin.

PAH is a debilitating progressive disease that causes a wide range of non-specific symptoms including, dyspnea, shortness of breath, chest pain, fatigue, generalized weakness and exertional syncope (Delcroix and Howard, 2015), severely affecting the patient's physical mobility, emotional and social well-being, ability to perform activities of daily living and overall quality of life. Pharmacological treatments are available to mitigate disease symptoms and slow disease progression, but treatment-related AEs, inconvenience and side effects can be treatment-limiting and negatively influence the patient's daily life (Delcroix and Howard, 2015).

The currently available pharmacologic treatments for PAH include calcium channel blockers, guanylate cyclase stimulators, endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, and prostanoids and prostacyclin agonists. Prostanoids, such as TRE, are among the most effective medications for the treatment of PAH. However, they are limited by the need for inconvenient and frequent drug administration and dose-limiting side effects (Thenappan et al., 2018).

2.1. Study Rationale

Treprostinil palmitil (TP) is an inactive prodrug of treprostinil (TRE). TPIP is a dry powder for inhalation formulation of TP. TPIP is being developed for the treatment of PAH. TPIP is expected to provide extended release of TRE in the lung with the goals of less frequent and more convenient and consistent dosing while reducing the frequency and severity of dose-limiting side effects associated with the currently approved forms of TRE. TP has been previously studied in healthy volunteers as an inhalation suspension (treprostinil palmitil inhalation suspension, TPIS), in single doses up to 340 µg (Study INS1009-101), and TPIP has been previously studied in a single ascending dose/multiple ascending dose (SAD/MAD) study in healthy volunteers (Study INS1009-102).

No studies of TP or TPIP have been conducted in participants with PAH. Study INS1009-201 is an open label, non-randomized, single- dose study designed to evaluate the safety, pharmacokinetics (PK), and pharmacodynamic (PD) effects of a single dose of TPIP in participants with PAH. An optional EUT period was added to maximize participant convenience and accessibility.

2.2. Background

Treprostinil is a tricyclic benzidene analogue of prostacyclin. As such, TRE has vasodilatory and anti-platelet activity within the pulmonary vascular system, thereby reducing blood flow resistance and improving the clinical state, functional class, exercise capacity, and quality of life of patients with PAH (Vachiery and Naeije, 2004).

Treprostinil has a high potency but is short-lived in the body and must be administered by continuous IV or SC infusion, or given multiple times per day by inhaled or oral routes. At present, TRE is available in the United States in formulations of IV or SC infusion (Remodulin Package Insert, 2018), oral extended-release tablets (Orenitram Package Insert, 2019), and inhalation solution (Tyvaso Package Insert, 2017) to treat PAH. The clinical experience with TRE suggests that most of the AEs experienced are related to its effects on prostanoid metabolism (e.g., headache, nausea, diarrhea, flushing, bleeding, and hypotension). Dose-limiting side effects correlate to systemic plasma concentrations of TRE.

Treprostinil palmitil is a hexadecyl ester prodrug of TRE. In the lung, TP is hydrolyzed by esterase to TRE and hexadecanol. TPIP is a dry powder formulation of TP designed to provide sustained release of TRE in the lung over a prolonged period, thus providing prolonged vasodilation in the lung vasculature. This effect was demonstrated in a rat acute hypoxia model that showed a maximal reduction in PAP through the 3-hour monitoring limit with TP, while the effect of inhaled TRE started to diminish by 1 hour and was completely gone after approximately 2.5 hours. The prolonged lung exposure and pharmacological action of TRE achieved with sustained release from the prodrug TP aims to reduce both dosing frequency and side effects driven by fluctuations of plasma levels of TRE.

Treprostinil palmitil was well tolerated in rats and dogs following 16-week once-daily inhalation. At no observed adverse effect level (NOAEL) doses, the plasma C_{max} and AUC of TRE at steady

state in rats (2000 µg/kg/day) were 11 ng/mL and 73 ng*h/mL, respectively, and in dogs (250 µg/kg/day) were 1.2 ng/mL and 13 ng*h/mL, respectively.

Thus far, TP has been studied in 2 Phase 1 studies of healthy participants: An SAD study of TPIS (Study INS1009-101) and an SAD/MAD study of TPIP (Study INS1009-102). Single doses of up to 675 µg and multiple doses of up to 225 µg for 7 days were administered to healthy participants. Overall, TP was well tolerated, with largely mild treatment-emergent adverse events (TEAEs) and an adverse effect profile consistent with that of inhaled prostacyclin analogs. Treprostinil exposures increased approximately dose-proportionately, were similar between TPIS and TPIP, and showed no accumulation with QD dosing. Doses of TP achieved were several-fold higher than label-indicated target dose of inhaled treprostinil (54 µg). When comparing TPIS to inhaled treprostinil, TP had a 10-fold lower maximum plasma concentration (89.0 pg/mL vs. 958 pg/mL) and a markedly longer half-life (5.69 hours vs. 0.485 hours) than inhaled treprostinil at the molar equivalent dose. Half-life of TP was even longer with TPIP, ranging from 8.67 to 11.6 hours. These differential PK of TP may offer therapeutic advantages over treprostinil with the need for less frequent administration (QD vs QID), fewer adverse effects, and potentially improved efficacy with higher tolerated dose.

Additional information regarding the results of non-clinical and clinical studies of TP are provided in the Investigator's Brochure.

2.3. Benefit/Risk Assessment

Detailed information about the known and expected benefits and risks and reasonably expected TEAEs for TPIP from clinical and non-clinical studies may be found in the Investigator's Brochure.

2.3.1. Risk Assessment

There is no TPIP experience in participants with PAH; however, the active component, TRE, like other prostanoids and their agonists, has a well-characterized safety profile. This will help enable participants to be adequately monitored during the study.

Insmed has conducted a SAD study of TPIS in healthy volunteer participants, with safety and tolerability findings similar to those of other prostanoids (Study INS1009-101). In this study, 32 TEAEs were reported for 11 of 18 participant who received TPIS. No fatal TEAEs were reported and no TEAEs led to the withdrawal of participants. One participant who received a single dose of TPIS containing 340 µg of TP experienced several interrelated AEs that culminated in 2 TEAEs of severe and life-threatening intensity, as judged by the Investigator. The Investigator believed a severe TEAE of micturition syncope was precipitated by a TEAE of chest pain, which was assessed as probably related to the study IMP and increased vagal tone during micturition. Follow-up evaluation by an external cardiologist reveled that the participant had Tachy-Brady syndrome. A serious adverse event (SAE) of cardiac pause/nodal arrhythmia was reported for this participant and assessed as probably related to TPIS. Beyond this event, 7 TEAEs were assessed as being of moderate intensity and 23 TEAEs to be of mild intensity.

The most frequently reported TEAEs among participants receiving TPIS were cough (5 events for 5 participants), dyspnea (4 events for 4 participants), and throat irritation (4 events for

4 participants). Other TEAEs reported for more than 1 participant receiving TPIS included nausea (3 events for 3 participants) and headache (2 events for 2 participants).

There was a dose-related trend in the incidence of TEAE reporting with increasing dose levels of TPIS: 5 TEAEs were reported for 2 participants after receiving a single TPIS dose containing 85 µg of TP, 7 TEAEs were reported for 4 participants after receiving a single TPIS dose containing 170 µg of TP, and 20 TEAEs were reported for 5 participants after receiving a single TPIS dose containing 340 µg of TP.

Safety results from a recently conducted SAD/MAD study of TPIP in healthy volunteer participants (Study INS1009-102) support the TPIP dosing and management of participant safety for this study. In this study, TPIP was generally safe and well tolerated. TEAEs reported with TPIP were consistent to those seen with other inhaled prostanoid therapies. The majority of TEAEs were judged by the Investigator to be of mild intensity; there were few moderate TEAEs and no severe TEAEs across the study. No participants reported AEs of severe intensity, and no SAEs were reported. There was 1 participant in the MAD panel who discontinued after 2 doses. TEAEs were more frequent with increasing TPIP doses. In the MAD panel, participants titrated from TPIP 112.5 µg QD to 225 µg QD experienced fewer TEAEs than those who received 225 µg QD at treatment initiation, and all TEAEs were of mild severity.

Nonserious adverse events (AEs) observed in clinical studies to date are known for the pharmacological class of prostacyclin vasodilators and are considered expected for TPIP. No serious adverse reactions are considered expected for TPIP. Please refer to the Reference Safety Information in Section 6.1 of the Investigator's Brochure.

Risks inherent in study procedures and in the inpatient treatment period will be managed per Investigator and institutional processes. It is possible that the RHC-dependent Baseline parameters may indicate that the participant does not meet study inclusion criteria, may meet exclusion criteria, or is otherwise not suitable for study participation; in this case the Investigator may end the RHC procedure and not administer TPIP.

In general, an RHC is left in place for 30 to 60 minutes to take necessary measurements. This study requires the RHC to be in place for approximately 24 hours. Excess risks with prolonged placement of the RHC may include but not be limited to dislodging of the RHC, infection, bleeding, clot formation, and participant discomfort.

2.3.2. Benefit Assessment

TPIP is being developed for the treatment of PAH. TPIP may or may not result in beneficial effects for participants with PAH by providing extended release of TRE in the lung with less frequent and more convenient dosing.

2.3.3. Overall Benefit: Risk Conclusion

Although participants may or may not benefit individually from this study, risks to their well-being will be carefully monitored and managed throughout their participation. Insmed considers the risks to be appropriate to the value of the knowledge gained in this study about the characteristics of this promising therapy. The well-characterized safety profile of TRE and the

continued safety monitoring by both the Investigator and SRC (in the inpatient treatment period, observation period, and optional EUT period, if applicable) will minimize risk to participants. Most TEAEs observed with exposure to this drug are events known to be associated with prostanoids and their agonists. Study inclusion and exclusion criteria will help to ensure that only appropriate participants are enrolled. Risks involved with study procedures and settings will be managed by the relevant Investigator and institutional processes.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	Primary
• To evaluate the safety and tolerability of single doses of TPIP in participants with PAH	• Frequency of TEAEs
Secondary	Secondary
• To evaluate the effects of single doses of TPIP on PVR in participants with PAH over the first 24 hours following administration	• Change from Baseline in PVR at 8 and 24 hours after TPIP administration
• To evaluate the PK of TRE in participants with PAH	• C_{max}, t_{max}, $AUC_{t1–t2}$, $AUC_{0–\infty}$, $t_{1/2}$ of TRE in plasma
Exploratory	Exploratory
• To evaluate the PD effects of single doses of TPIP in participants with PAH over 24 hours following administration	• Change from Baseline in PVR, PAP, RVP, RAP, CO, oxygen consumption, MVO_2, SpO_2, heart rate, systemic blood pressure, hemoglobin, at selected time points after TPIP administration
• To evaluate the PD effects of NO challenge in participants with PAH over 24 hours following administration	• Change from Baseline in PVR, PAP, RVP, RAP, CO, oxygen consumption, MVO_2, SpO_2, heart rate, systemic blood pressure, hemoglobin, at selected time points after NO challenge
• To evaluate the effect of single doses of TPIP on selected biomarkers in participants with PAH over 24 hours following administration	• Change from Baseline in selected biomarker concentrations at selected time points after TPIP administration

• To evaluate changes in clinical laboratory parameters in participants with PAH after TPIP administration	• Clinically relevant change from Baseline in hematology, coagulation, and clinical chemistry parameters (Section 10.2, Table 8)
• To evaluate the PK of TP in participants with PAH • To evaluate the PK of TRE in participants with PAH	• Plasma PK parameters of TP, such as C_{max}, t_{max}, $AUC_{t1–t2}$, $AUC_{0–\infty}$, $t_{1/2}$, CL/F and Vd/F • Plasma PK parameters of TRE, such as C_{max}, t_{max}, $AUC_{t1–t2}$, $AUC_{0–\infty}$, $t_{1/2}$, CL/F and Vd/F
• To evaluate the effects of TPIP on resting respiratory gas exchange in participants with PAH[a]	• Change from Baseline in respiratory rate, minute ventilation, VCO_2, ETO_2, $ETCO_2$, SpO_2 over 24 hours after TPIP administration
• To evaluate the effects of TPIP on parameters of right ventricular function in participants with PAH as measured by transthoracic echocardiogram[b]	• Change from Baseline in LVEF, TVR maximum velocity, TAPSE, and end diastolic right ventricular volume at 2 to 8 hours after TPIP administration
• To evaluate the effects of TPIP on pulmonary vasculature and blood flow parameters in participants with PAH as measured by pulmonary CT scan[c]	• Change from Baseline in total blood volume, blood volume in vessels < $5mm^2$ at 4 to 8 hours after TPIP administration

[a] Respiratory gas exchange testing optional at Investigator discretion
[b] Echocardiogram optional at Investigator discretion
[c] Pulmonary CT scan optional at Investigator discretion
$AUC_{0–\infty}$ = area under the concentration time curve from time zero to infinity; AUC_{t1-t2} = area under the concentration time curve from time zero to last sampling time point with measurable concentration; C_{max} = maximum observed concentration after drug administration; CL/F = apparent total clearance; CO = cardiac output; CT = computerized tomography; $ETCO_2$ = end tidal carbon dioxide concentration; ETO_2 = end tidal oxygen concentration; LVEF = left ventricular ejection fraction; MVO_2 = mixed venous oxygen saturation; PAH = pulmonary arterial hypertension; PAP = pulmonary arterial pressure; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PVR = pulmonary vascular resistance; SpO_2 = arterial blood oxygen saturation; TAPSE = tricuspid annular plane systolic excursion; TEAE = treatment emergent adverse event; TP = treprostinil palmitil; TPIP = treprostinil palmitil inhalation powder; TRE = treprostinil; TVR = tricuspid valve regurgitation; t_{max} = time of maximum observed concentration following drug administration; $t_{1/2}$ = elimination half-life; Vd/F = apparent volume of distribution at terminal phase; VCO_2 = carbon dioxide production

3.1. Exploratory Objectives and Endpoints for the Optional Extended Use Treatment Period

Objectives	Endpoints
Exploratory	Exploratory
• To evaluate the safety and tolerability of TPIP in participants with PAH	• Frequency of TEAEs during EUT
• To assess the effect of TPIP on exercise capacity	• Change in 6MWD distance from study Baseline to EUT Week 16

6MWD = 6-minute walk distance; EUT = extended use treatment period; PAH = pulmonary arterial hypertension; TEAE = treatment emergent adverse event; TPIP = treprostinil palmitil inhalation powder

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2a, open label, non-randomized study to assess the safety, tolerability, PD effects and PK of TPIP administered to participants with WHO Group 1 PH (PAH). This is the first patient study of TPIP. Each participant will receive a single dose of TPIP. The first participant will receive a dose containing 112.5 µg. Subsequent participants will receive 80 µg, or a combination of capsules containing 80 µg, 160 µg, and 320 µg of TP, based on SRC recommendations. The TP dose level for each subsequent participant will be determined following review and adjudication of all available safety, PK, and PD data from the previous participant(s) by the SRC (Section 10.1.7). There is an optional extended-use period for 16 weeks in participants who have completed the core, single-dose period.

This is a "proof of mechanism" study designed to investigate the following:

1. The safety and tolerability of TPIP in participants with PAH,
2. The relationship between the PK and PD effects of TPIP in participants with PAH, and
3. The duration of the PD effects of a single dose of TPIP in participants with PAH.

The cardiopulmonary and overall functional status of participants with PAH can be labile and medical instability can develop quickly. The study is designed to provide maximal safety and minimal risk to participants. As such, there considerable flexibility built into the protocol to allow Investigator discretion with the frequency, timing, and/or conduct of PD and PK assessments to ensure participant safety. Because the study requires an overnight inpatient treatment period, institutional requirements for elective inpatient admissions, which may vary from site to site, will be followed.

For individual participants, the study will consist of an outpatient screening period lasting up to 30 days. The inpatient treatment period will start on Study Day 1 and is expected to last overnight into Study Day 2. Outpatient PK sampling and safety follow-up at 48 (± 4) hours post TPIP dose will extend into Study Day 3. A remote safety follow-up visit is scheduled for Study Day 30 (± 2 days). The 48 hour PK visit will also include safety assessments including ECG, clinical laboratory evaluations, vital signs, physical examination, and AE collection (Table 1). The safety follow-up period will conclude with a remote (telephone or telemedicine) visit on Study Day 30 (± 2 days). The screening, treatment, and follow-up periods for the core, single-dose portion of the study are expected to be 62 days or less. An EUT period of 16 weeks will be optional for participants that complete the single-dose period, followed by a 30 day follow-up (± 3 days). This extends study participation to 142 days after enrollment in the EUT period.

4.1.1. Screening Period

The initial screening period will be up to 30 days. Required screening assessments are shown in Table 1. Participants who fail one or more screening assessments may be re-screened twice at the Investigator's discretion in order to meet study entry criteria. See Section 5.4 for additional information regarding participants who fail screening and/or are re-screened.

Participants who enter the optional EUT period more than 30 days after beginning the single-dose period (e.g., beyond the initial 30 day follow-up period) will be screened to ensure they continue to satisfy inclusion and exclusion criteria. Extended use treatment period screening assessments are shown in Table 5.

4.1.2. Inpatient Treatment Period

4.1.2.1. Baseline Procedures and Assessments

The inpatient treatment period will be on Study Days 1 and 2. The participant may be required to undergo pre-admission assessments required by the Institution for elective admission, for example testing for common infectious pathogens. Signature of institutional elective admission documents and consents to procedures may be required. Data from required institutional assessments and consents will not be routinely collected as part of study data unless they pertain to a relevant AE or study endpoint.

Participants will be admitted to an inpatient care setting such as an ICU, cardiac catheterization laboratory or other similar setting. They will have Baseline laboratory and safety assessments as shown in Table 2. A nitric oxide challenge will be performed to screen for vasoreactivity of pulmonary vasculature. An RHC will be placed for Baseline assessment of cardiopulmonary hemodynamics prior to TPIP administration and intermittent assessments of cardiopulmonary hemodynamics for 24 hours following TPIP administration. Institutional procedures and protocols for placement, care, monitoring, and removal of the RHC will be carried out but will not be collected as study data unless relevant.

Some procedures and assessments for exploratory endpoints may not be offered at all sites. Participants will be asked to give informed consent only to those procedures that are being conducted by their Investigator at their site. These procedures include the following:

- Transthoracic echocardiogram at Baseline and during a 2 to 8 hour window after TPIP administration (Table 4).
- Pulmonary computerized tomography (CT) scan at Baseline and during a 4 to 8 hour window after TPIP administration (Table 4).
- Resting respiratory gas exchange assessment at Baseline and intermittently after TPIP administration for up to 24 hours (Table 4). Resting respiratory gas exchange assessments will be standardized, with all participating investigators using similar equipment and procedures.

For example, an Investigator who is doing only RHC and resting respiratory gas exchange assessments for this study will obtain informed consent for those procedures only and will not offer or ask the participant for informed consent for transthoracic echocardiogram or pulmonary CT scan as part of this study.

Following completion of all Baseline assessments, including Baseline blood draws for PK and PD biomarkers (Table 3), the prescribed single dose of TPIP will be administered (Table 2).

4.1.2.2. Post-TPIP Administration

Following TPIP administration, participants will have intermittent safety, clinical laboratory, PK, and PD assessments, as specified in the SoA (Table 2, Table 3, and Table 4). The study is designed to allow maximum flexibility for interventions and assessments at the discretion of the Investigator and institutional policies and procedures to ensure participant safety. At any time, the Investigator has the option to discontinue assessments for participant safety or tolerability reasons. Additional laboratory and/or hemodynamic assessments may be performed as deemed necessary for participant safety. Following completion of scheduled events, the Investigator has the option of continued laboratory and/or hemodynamic monitoring as deemed appropriate for participant safety.

If, in the interest of participant safety, the Investigator omits scheduled assessments/procedures or performs additional assessments/procedures, the reason for doing so must be reported on the CRF as an AE in order to avoid a protocol violation.

Following completion of protocol-required assessments and removal of the RHC, the participant will be discharged from the inpatient setting when deemed safe by the Investigator. Investigator and institutional usual care protocols for participant discharge and follow-up for an RHC procedure will apply.

4.1.2.3. Post-discharge Outpatient Visits for PK Sampling and Safety Follow-up

The participant will be required to return as an outpatient for the 48 (± 4) hour post-TPIP administration PK sample. Additional safety assessments such as ECG, physical examination, vital signs, AE collection, and clinical laboratory evaluations will be completed at the 48 hour visit. Female participants who are women of child-bearing potential (WOCBP) will be given a self-administered pregnancy test kit with instructions to self-administer the test and report the results on the day of the Study Day 30 safety follow-up visit (Section 4.1.3).

4.1.3. Safety Follow-up

A remote (telephone call or telemedicine) safety follow-up visit is scheduled for Study Day 30, at which time participants who are WOCBP will also be asked to report the results of the self-administered pregnancy test they were given at the 48 hour post-TPIP follow-up visit (Section 4.1.2.3, Table 1).

4.1.4. Optional Extended Use Treatment Period

All participants will be allowed to enter the optional 16 week EUT period after the completion of the inpatient treatment period and final PK sample collection. Entry into the optional EUT period will be at participant and Investigator discretion. A gap between the inpatient treatment period and EUT period is expected, but not required, and can be up to 6 months.

After collection of the final PK sample, all participants will be allowed optional continued access to IMP for 16 weeks (includes a 3-week titration period) from first administration in the EUT period. At the Investigator's discretion, participants may undergo a study drug taper for up to 2 weeks after the Week 16 visit to help facilitate a safe withdrawal from study drug.

Participants will be screened to ensure they meet inclusion and exclusion criteria if they enter the EUT period more than 30 days after beginning the single-dose period (e.g., beyond the initial 30 day follow-up period) (Table 5).

Participant in-clinic study visits will be scheduled for EUT Baseline (EUT Day 1), EUT Week 2, EUT Week 3, EUT Week 5, EUT Week 10, and EUT Week 16.

The CT scan will be performed according to instructions provided by the CT scan vendor.

There will be a second safety follow-up visit 30 days (± 3 days) after EUT Week 16 for participants who elect to enter the EUT period.

4.1.5. Open-label Extension Study

When available, participants may be eligible to enroll in a separate OLE study that will have a duration of approximately 2 years. Details of the planned OLE study will be provided in a separate protocol.

4.2. Scientific Rationale for Study Design

The study is designed to understand the safety and acute PK and PD effects of TPIP in participants with PAH, the intended patient population. Intensive monitoring via RHC in an appropriate inpatient setting is essential to understand how TPIP affects cardiopulmonary hemodynamics and to elucidate relationships between dose, PK, and PD effects. Some assessments and study activities for exploratory endpoints are considered optional depending on Investigator preference and/or based on study site capabilities and procedures (Table 4).

4.3. Justification for Dose

4.3.1. Inpatient Treatment Period (Single-dose)

Treprostinil palmitil has been previously studied in healthy volunteer participants as a liquid suspension for inhalation (TPIS) and has now been formulated as a dry powder for oral inhalation (TPIP). Data from pre-clinical pharmacology and safety studies supported the initiation of human studies with TPIS. Preclinical studies in rats and dogs showed that the plasma kinetics of TRE and TP after dosing with TPIP are similar to those of TPIS. Additional clinical PK and safety data from healthy participants after SAD and MAD dosing with TPIP supported the chosen study design and dose. For further information on the non-clinical pharmacology and safety studies of TPIS and TPIP, please refer to the Investigator's Brochure.

The current study utilizes the clinical experience of TPIS from Study INS1009-101 in healthy volunteer participants and the INS1009-102 SAD/MAD study of TPIP in healthy volunteer participants. In Study INS1009-101, doses of TPIS were administered in multiples of 85 µg TP to include 170 µg (2 × 85 µg) and 340 µg (4 × 85 µg) of TP. The systemic exposure for TRE at 340 µg TP was low (AUC < 2.5 ng*h/mL) with an elimination $t_{1/2}$ of approximately 7 hours.

Data from the INS1009-102 SAD/MAD study of TPIP reinforced the study design and informed maximum dosage for the optional extended use portion of the study (Section 4.3.2). In the first SAD portion of INS1009-102 (SAD1), 18 participants were randomized to 1 of 3 TP dose levels

of TPIP: 112.5 µg, 225 µg, or 450 µg of TP (6 participants at each dose). Treprostinil peak concentrations in the SAD portion were attained at 1.5 to 3 hours post-dose; C_{max} and AUC were dose-dependent and approximately proportional to the increase of dose; and elimination $t_{1/2}$ was 8.7 to 11.6 hours. Total treprostinil exposure (AUC) of treprostinil was found to be dose proportional following a single administration of TPIP across the dose range of 112.5 µg to 675 µg.

Based on this Phase 1 study experience, the first participant will be dosed with 112.5 µg of TP. Subsequent participants will receive 80 µg of TP, or a combination of capsules containing 80 µg, 160 µg, and 320 µg of TP, based on SRC recommendations. Additional details on these doses may be found in Section 4.3.2. Single doses of up to 90 µg of Tyvaso have been administered in clinical studies of healthy volunteer participants (Tyvaso Package Insert, 2017).

Each participant will receive a single dose administration of TPIP. All available data (PD, PK, safety) from the first participant will be assessed and evaluated by the SRC. Following this evaluation, the SRC will determine if it is safe to continue the study, the TPIP dose level and any changes to safety PD and PK assessments for the second participant (Figure 3). This process will be repeated using the total accrued data of all completed participants prior to determining the TPIP dose for each subsequent participant. There will be no simultaneous dosing of inpatient participants; each participant will be treated as an individual case for evaluation. The TP dose level for each subsequent participant may be increased, held stable or lowered, depending on the accumulating data from previous participants up to a maximum of 640 µg. TPIP dosing may also be stopped at any dose level as determined by the SRC.

4.3.2. Optional Extended Use Treatment Period

Selection of once-daily inhalation of TPIP at 80 – 640 µg was based on clinical PK and safety data from healthy participants, predicted efficacious dose levels using pre-clinical data, safety margin from rat and dog NOAEL doses, and Tyvaso® clinical experience.

In Phase 1 studies, TRE PK was linear, and the systemic exposure was dose proportional. Single doses of up to 675 µg and multiple doses of up to 225 µg TPIP QD for 7 days were generally well tolerated. Most AEs observed were mild in severity and consistent with the safety profile of other prostanoid therapies.

Based on exposures following a single dose of TPIP 675 µg in Study INS1009-102, TRE exposures in this study are not anticipated to exceed those following administration of the currently approved treprostinil product, Remodulin®. Treprostinil exposures following a continuous IV infusion of 10 ng/kg/min Remodulin (C_{max} 1,470 pg/mL; AUC 25,690 pg*h/mL) are reported to be 2.1-fold and 4.7-fold higher, respectively, than those observed following administration of TPIP 675 µg (C_{max} 717 pg/mL; AUC 5,480 pg*h/mL) (Laliberte et al., 2004). Minimal accumulation was observed following repeat doses of TPIP 225 µg QD for 7 days, and since a lower maximum dose (640 µg) will be used in this study, TRE exposures are expected to be lower than those observed following single doses of TPIP 675 µg in Study INS1009-102.

Based on the findings above, the TPIP dose will range from 80 µg to 640 µg QD in this treatment period.

4.4. Study Completion

A participant will be considered to have completed the study if he/she has completed the Study Day 30 safety follow-up (shown in Table 1) and has not elected to enter the optional EUT period. A participant who has entered the optional EUT period will be considered to have completed the study if he/she has completed the EUT period safety follow-up (EUT Day 142). The study will be considered completed on the date of the last safety follow-up of the last participant in the study.

5. STUDY POPULATION

The study is expected to recruit approximately 6 to 10 participants at up to 12 centers with appropriate inpatient facilities. Eligible participants must have clinically stable disease, and participants may not be taking more than 2 medications from the following classes:

- Endothelin receptor antagonists (eg ambrisentan, bosentan, macitentan),
- Phosphodiesterase type 5 inhibitors (eg sildenafil, tadalafil)
- Guanylate cyclase stimulator (eg riociguat)

It is expected that the site will recruit appropriate potential participants according to the criteria in Section 5.1 and Section 5.2.

The study inclusion and exclusion criteria include thresholds of selected RHC and ECG parameters that must be met at Baseline or the participant will not be considered eligible for the study. In this case, the participant is to be reported as a Screen Failure (Section 5.4).

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if they meet all of the following criteria[a]:

Age:
1. Participant must be ≥ 18 years of age at the time of signing the informed consent.
Type of Participant and Disease Characteristics
2. Participants must have a diagnosis of WHO Group 1 PH (PAH) with etiology of idiopathic, heritable, drug/toxin-induced or connective tissue disease (CTD)-related PAH (Galie et al., 2016). 3. Prior PAH diagnosis, or diagnosis at Baseline if participant has not had a prior right heart catherization. 4. No change in pulmonary hypertension medications (e.g., ambrisentan, bosentan, macitentan, sildenafil, tadalafil, riociguat) or dosage for at least 30 days prior to Screening. 5. Documented predicted percent forced vital capacity (FVC) > 70% within 3 years of Screening. If not available, pulmonary function testing will be performed at Screening (Table 1). 6. Low or Intermediate risk, as per Investigator assessment of the European Respiratory Society/European Society for Cardiology (ERS/ESC) criteria (Galie et al., 2016). 7. Right heart catheterization at Baseline with the following hemodynamic findings: a. Mean pulmonary arterial pressure (mPAP) > 20 mmHg at rest, b. Pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg, and c. Pulmonary vascular resistance (PVR) of ≥ 3 Wood Units (WU)

Sex and Contraceptive/Barrier Requirements
8. Male participants: Male participants and their female partners of childbearing potential must agree to use highly effective contraception from Study Day 1 to at least 90 days after dosing. 9. Female participants: Women of child-bearing potential (WOCPB, defined as premenopausal, not surgically sterile for at least 3 months prior to Screening) must use a highly effective contraception method and agree to be tested for pregnancy from at Screening, Baseline, and 30 days after dosing. See Section 10.4 for contraceptive guidance.
Informed Consent
10. Capable of giving signed informed consent as described in Section 10.1.5 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

[a] Please note that participants who enroll in the optional EUT period beyond the initial 30 day follow-up period will be screened to confirm that they still meet inclusion/exclusion criteria. Please refer to Table 5.

5.2. Exclusion Criteria

Participants are excluded from the study if they meet any of the following criteria[a]:

Medical Conditions
1. Any PH other than idiopathic, hereditary, drug/toxin-induced, or connective tissue disease (CTD) associated PAH (e.g., congenital heart disease-associated PAH, portal hypertension-associated PAH, PH belonging to Groups 2 through 5) 2. Allergy, or documented hypersensitivity or contraindication, to the ingredients of treprostinil palmitil inhalation powder (TPIP) or treprostinil (TRE). 3. Previous intolerance to prostacyclin analogs or receptor agonists (e.g., selexipag) per Investigator discretion 4. History of anaphylaxis or previously documented hypersensitivity reaction to any drug per Investigator discretion 5. QTcF interval > 480 ms on resting ECG at Baseline 6. History of heart disease including left ventricular ejection fraction (LVEF) ≤ 40% or clinically significant valvular, constrictive, or atherosclerotic heart disease (myocardial infarction, etc) 7. Abnormal renal function (estimated glomerular filtration rate < 30 mL/min/1.73m^2) at Screening. 8. Active liver disease or hepatic dysfunction manifested as:

a. Elevated liver function test results (ALT or AST > 2 × ULN) at Screening

b. Bilirubin > 1.5 × ULN (isolated bilirubin > 1.5 × ULN; ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%) at Screening.

c. Known hepatic or biliary abnormalities, not including Gilbert's syndrome or asymptomatic gallstones at Screening.

9. History of HIV infection/positive HIV serology test result at Screening.
10. History of active/chronic Hepatitis B or C/ positive hepatitis B or C serology test result at Screening
11. History of abnormal bleeding or bruising.
12. Known or suspected immunodeficiency disorder, including history of invasive opportunistic infections (e.g., tuberculosis, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis) despite infection resolution, or otherwise recurrent infections of abnormal frequency, or prolonged infections suggesting an immune-compromised status, as judged by the Investigator.
13. Active and current symptomatic infection by SARS CoV 2. Additional COVID 19 restrictions per institutional guidelines (See also Section 10.1.3.1.3)
14. Participants with current or recent (past 4 weeks) lower respiratory tract infection (may be re-screened at appropriate time (Section 5.4)
15. History of malignancy in the past 5 years, with exception of completely treated in situ carcinoma of the cervix and completely treated non-metastatic squamous or basal cell carcinoma of the skin.

Concomitant Therapy

16. Participants receiving triple combination therapy for PAH consisting of endothelin receptor agonists, phosphodiesterase type 5 inhibitors, and guanylate cyclase stimulators (riociguat).
17. Participants receiving prostanoids/prostacyclin agonists
18. Other prior/concomitant therapies are allowed/disallowed at the Investigator’s discretion

Prior/Concurrent Clinical Study Experience

19. Have participated in any other interventional clinical studies within 30 days of Baseline

Diagnostic assessments

20. Any clinically significant abnormal laboratory, value, test result, or physical examination finding at Screening; diseases or diagnoses/disorders that, in the

	opinion of the Investigator, may put the participant or others at risk by participating in the study, interfere with the participant's treatment and assessment, or influence the results of the study; or have compliance issues with the study.
Other Exclusions	
	21. Current or history of substance and/or alcohol abuse per Investigator assessment 22. Current user of cigarettes or e-cigarettes 23. Pregnant or breastfeeding.

[a] Please note that participants who enroll in the optional EUT period beyond the initial 30 day follow-up period will be screened to confirm that they still meet inclusion/exclusion criteria. Please refer to Table 5.

5.3. Lifestyle Considerations

No lifestyle restrictions are required.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study because they did not meet all inclusion criteria or meet one or more exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened twice at the Investigator's discretion. If a participant can be rescreened, the PI is to consult with the Medical Monitor to determine whether some or all of the screening assessments must be repeated. Rescreened participants will sign a new ICF and will be assigned a new participant number.

5.5. Criteria for Temporarily Delaying Inpatient Treatment Period

Following successful screening and meeting of study eligibility criteria, the inpatient treatment period and RHC procedure must be scheduled without delay.

The scheduled treatment period may be temporarily delayed no longer than 28 days by the Investigator in consultation with the Medical Monitor for valid reasons. Examples of valid reasons for delaying the treatment period may include such things as a life event for the participant (eg death in the family), local public health emergency (e.g., COVID 19 outbreak), site facility issues (e.g., catheterization lab or ICU bed availability), or pending TPIP dosing directives from the SRC.

A temporary delay in the scheduled inpatient treatment period for a valid reason may result in previously met Inclusion Criteria that rely on a time window to be not met. This is not considered to be a Screen Failure. In this case, the Investigator should consult with the Medical

Monitor to identify which screening tests need to be conducted or repeated to ensure that the participant meets study inclusion criteria and can safely participate in the study.

Deterioration of the participant's medical condition is not a valid reason to delay start of the inpatient treatment period. In some cases, delaying the inpatient treatment period may cause the participant to meet one or more exclusion criteria (e.g., participant develops a lower respiratory infection). In this case the participant should be considered a Screen Failure and Section 5.4 applies.

6. STUDY IMP AND CONCOMITANT THERAPY

Study IMP is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study IMP Administered

6.1.1. Inpatient Treatment Period (Single Dose)

A single dose of TPIP will be used in the inpatient treatment period, as listed below. A dose may consist of a single capsule or of multiple capsules administered in succession.

Name of Treatment	Dose	Supplied Formulation	Route and Frequency of Administration
Treprostinil palmitil inhalation powder (TPIP)	One or more single actuation capsules	*First study participant only:* Single actuation capsules containing 112.5 µg TP per 7.5 mg powder	Inhalation; single dose after Baseline assessments
Treprostinil palmitil inhalation powder (TPIP)	One or more actuation capsules (80 µg, 160 µg, 240 µg, 320 µg, 400 µg, 480 µg, or 640 µg)	Dry powder single actuation capsules containing 80 µg, 160 µg, or 320 µg	Inhalation; single dose after Baseline assessments

QD = once daily

6.1.2. Optional Extended Use Treatment Period

The IMP used in the EUT period will be capsules containing 1 of 3 dosage strengths of TPIP (80 µg, 160 µg, or 320 µg). IMP should be taken around the same time every day. Administration of IMP will be via inhalational dry powder packaged in single actuation capsules. One or 2 capsules will be administered for each dose. Administration of 2 capsules should be done sequentially. Each TPIP capsule contains 8 mg, 16 mg, or 32 mg of dry powder containing 80 µg, 160 µg, or 320 µg of the TP prodrug, respectively.

Name of Treatment	Dose	Supplied Formulation	Route of Administration
Treprostinil palmitil inhalation powder (TPIP)	One or two single actuation capsules (80 µg, 160 µg, 240 µg, 320 µg, 400 µg, 480 µg or 640 µg QD)	Dry powder single actuation capsules containing 80 µg, 160 µg, or 320 µg	Inhalation (QD)

QD = once daily

6.1.3. Medical Devices

In the planned clinical study, the TPIP will be administered by oral inhalation using a Plastiape capsule-based Dry Powder Inhaler (RS 01 Mod 7). A Type III Drug Master File is filed at the US FDA and the RS01 inhaler is classified as a Class I medical device. The Instructions for Use of the device document is provided separately as an Appendix to the Pharmacy Manual.

All device deficiencies (including malfunction, use error, and inadequate labeling) shall be documented and reported by the Investigator throughout the clinical investigation (Section 8.3.7) and appropriately managed by Insmed.

6.2. Preparation/Handling/Storage/Accountability

Insmed Incorporated will provide the Investigator and clinical unit with adequate quantities of TPIP capsules. For 80 µg, 160 µg, and 320 µg doses, HDPE bottles will be closed with the desiccant placed inside the bottle, and induction sealed. The powder will be administered by oral inhalation using a Plastiape capsule-based Dry Powder Inhaler.

6.2.1. Inpatient Treatment Period (Single-dose)

Directions for preparation and administration of the TPIP dose to the participant are provided in a separate document as an Appendix to the Pharmacy Manual for the single-dose Inpatient Period.

All study IMP must be stored according to the labeled instructions in a secure cabinet or room with access restricted to necessary clinic personnel. The site will be required to keep a temperature log to establish a record of compliance with storage conditions. Current stability data supports the shelf life assigned to TPIP when stored at 2 to 8 °C.

- The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study IMP received and any discrepancies are reported and resolved before use of the study IMP.
- Only participants enrolled in the study may receive TPIP and only authorized site staff may supply or administer it. All TPIP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
- The Investigator, institution, and/or pharmacist or designee is responsible for study IMP and dosing devices accountability, reconciliation, and record maintenance (e.g., receipt, reconciliation, and final disposition records).
- Study IMP and dosing device accountability records will be maintained for all clinical supplies. All transactions will be recorded on the drug and dosing device accountability records including shipment receipts and study participant doses. All transactions will be recorded on a real-time basis.
- The Investigator/site will maintain detailed documentation of the number and identification of bottles and dispensing units of TPIP with copies of these documents

to be provided to Insmed at the end of the study. All used and unused study IMP and dosing devices will be maintained by the site until inventoried by the study monitor. Upon completion of the study IMP and dosing device inventory by the study monitor, used and any unused study IMP and dosing devices will be disposed of in accordance with instructions provided to sites and according to site destruction policies. Documentation of destruction must be provided to Insmed.

- Further guidance and information for the final disposition of unused study IMP supplies can be obtained from Insmed.

6.2.2. Optional Extended Use Treatment Period

Directions for preparation and administration of IMP to the participant in-clinic are provided in the Pharmacy Manual for the optional EUT period. Directions for preparation and administration of IMP for home use will be provided to the participants.

Only participants enrolled in the study may receive IMP, and only authorized study personnel may supply IMP. All IMP must be stored according to the labeled instructions with access restricted to necessary clinic personnel. The site will be required to keep a temperature log to establish a record of compliance with storage conditions. Refer to the Pharmacy Manual for the optional EUT period for shelf-life and storage conditions.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for IMP and dosing devices accountability, reconciliation, and record maintenance (e.g., receipt, reconciliation, and final disposition records). Directions for storage, handling, accountability, and destruction are provided in the Pharmacy Manual for the optional EUT.

6.3. Measures to Minimize Bias: Randomization and Blinding

Not applicable.

6.4. Study Intervention Compliance

6.4.1. Inpatient Treatment Period (Single Dose)

Study participants will receive the TPIP dose directly from the Investigator or designee, under medical supervision, in an appropriate inpatient setting. The date and time of the dose administered will be recorded in the source documents. The dose of TPIP and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the TPIP.

6.4.2. Optional Extended Use Treatment Period

At each in-clinic visit, participants will be dispensed adequate IMP to allow for daily dosing. When participants are dosed at the site, IMP administration will be overseen by study site personnel. The date and time of each dose self-administered in the clinic will be recorded in the source documents. The dose of IMP and study participant identification will be confirmed at the time of dosing by a member of the study site personnel.

When participants administer IMP at home, compliance with IMP will be assessed at each in-clinic visit. Participants will record their daily dose on paper dosing diaries. Compliance will be assessed by direct questioning, review of participant dosing diaries, and counting of returned capsules during the site visits. Participants will return unused capsules and used study capsules and devices to the study site at each in-clinic visit. Participants who undergo a study drug taper will return unused capsules and used capsules and devices to the study site at a follow-up visit. Unused capsules should be returned in the bottle they were dispensed in. Deviation(s) from the prescribed dosage regimen should be recorded.

A record of the quantity of capsules dispensed to and administered by each participant must be maintained and reconciled with study drug logs and participant dosing diaries. Study drug start and stop dates, including dates for study drug interruptions and/or dose reductions will also be recorded.

6.5. Dose Modification

Dose modification is part of the study design and is described in detail in Section 4.3 and Section 1.3.2.

6.6. Continued Access to Study Intervention After the End of the Study

Not applicable.

6.7. Treatment of Overdose

An overdose is defined as the participant receiving any TPIP in excess of their assigned dose as predetermined by the SRC (Section 4.3). An overdose itself is not an AE. However, if the overdose results in clinical signs and symptoms, it requires expedited reporting as if it is an SAE. The Investigators must refer to the relevant documents for detailed information regarding warnings, precautions, contraindications, AEs, and other significant data pertaining to the study IMP. Such documents may include, but are not limited to, the Investigator's brochure.

In the event of an overdose, the Investigator must:

- Contact the Medical Monitor within 24 hours.
- Evaluate the participant to determine, in consultation with the Medical Monitor, how to proceed with treatment period procedures and assessments.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until TP or TRE is likely to be sufficiently metabolized and/or excreted and/or can no longer be detected systemically. The frequency and duration of plasma sampling from the last dose of TPIP must be determined by the Investigator in conjunction with the study team and Medical Monitor.
- The overdose must be fully documented (e.g., quantity of the excess dose, duration of the overdose, how it happened) in the CRF.

6.8. Concomitant Therapy

Any medications, treatments, or therapies that the participant is receiving at Baseline (Study Day 1) or receives during the study (Study Day 1 through end of study [EOS]) are considered concomitant therapy and will be collected and documented in the study CRF.

Documentation includes the name of the therapy, with the reason for use, the dates of administration including start and end dates, and dosage information including dose and frequency.

Prior medications are those medications taken before the first dose of study IMP. A medication that starts prior to first dose but continues after the first dose of study IMP is classified both in prior and concomitant medications. Any procedures performed from Day 1 through EOS are considered concomitant procedures and will be collected and documented in the study CRF.

The Medical Monitor must be contacted if there are any questions regarding concomitant or prior therapy.

For participants who enroll in the EUT period, new concomitant therapy for the period from the single-dose Study Day 30 follow-up until the enrollment in the EUT will be collected during participant's screening for the EUT.

6.8.1. CYP2C8 Inhibitors

Use of CYP2C8 inhibitors may increase the systemic exposure to TRE and should be avoided prior to initiation of study drug administration. Should the use of any of these medications within the specified pre-Baseline window or during the study be considered essential, the Investigator should consult the study Medical Monitor prior to dosing.

Table 7: Windows for CYP2C8 Inhibitor Medications

Medication	Minimal Time from Last Dose to Baseline
Gemfibrozil	1 day
Trimethoprim	1 week
Montelukast	3 days
Clopidogrel	3 days

7. DISCONTINUATION OF STUDY IMP AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study IMP

7.1.1. Single-dose Period

This is a single dose period; not applicable.

7.1.2. Optional Extended Use Treatment Period

If study drug is permanently discontinued, the participant will be encouraged to participate in their remaining study visits. See Table 6 for data to be collected at the time of discontinuation of IMP and follow-up. If a participant discontinues the study and needs to be started on another PAH medication, the Investigator should contact the Medical Monitor.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons.

At the time of discontinuing from the study after study drug administration, if possible, an early discontinuation evaluation should be conducted to maximize participant safety. This final evaluation and the reason for participant withdrawal must be documented in the CRF.

The participant will be permanently discontinued both from the study drug and from the study at that time.

If the participant is discontinued from the study due to an SAE, the Investigator will follow the participant until the Investigator deems that the SAE has resolved or stabilized.

The Investigator may withdraw the participant from the study due to absence of a PD response to TPIP. Lack of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the PK and PD assessments.

If the participant withdraws consent for disclosure of future information, Insmed may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled follow-up visits and is unable to be contacted by the study site.
The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of

maintaining the assigned visit schedule and ascertain whether or not the participant wishes to continue in the study.

- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts must be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered lost to follow-up and to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants, including those who did not get study IMP. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Insmed personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1.13.2).

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in Table 1, Table 2, Table 3, Table 4, Table 5, Table 6.

All screening evaluations must be completed and reviewed to confirm that potential participants meet eligibility criteria prior to scheduling the study RHC procedure and inpatient admission. The RHC procedure and inpatient admission must be scheduled for as soon as possible once the participant's eligibility for the study is confirmed by screening. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (e.g., previous RHC, previous echocardiogram, previous 6MWD test) and obtained before signing of the ICF may be utilized for screening or Baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frames defined either in the inclusion and exclusion criteria in Section 5 or in the SoA (Section 1.4).

For participants who do not elect to enter the EUT period, the maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required is expected to be approximately 140 mL and will not exceed 200 mL. Approximately 80 mL will be required for PK sampling over 48 hours and approximately 20 mL for biomarker sampling. Safety and screening blood samples will require approximately 20 to 30 mL. Blood loss from the RHC procedure is anticipated to be negligible.

For participants who do elect to enter the optional EUT period within the 30 day follow-up window in the single-dose period, there is no anticipated blood collection. For participants who elect to enter the optional EUT period after the 30 day follow-up in the single-dose period, Safety and screening blood samples will require approximately 20 to 30 mL. Blood loss from the RHC procedures is anticipated to be negligible.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples at the Investigator's discretion.

At any time, the Investigator has the option to discontinue assessments for participant safety or tolerability reasons. Additional laboratory, PK, and/or hemodynamic assessments may be performed as deemed necessary for participant safety. Following completion of scheduled events, the Investigator has the option of continued laboratory and/or hemodynamic monitoring as deemed appropriate for participant safety. If, in the interest of participant safety, the Investigator omits scheduled assessments/procedures or performs additional assessments/procedures, the reason for doing so must be reported on the CRF as an AE in order to avoid a protocol violation.

8.1. Pharmacodynamic Assessments

The results of each individual participant's PD assessments will contribute to the dosing decision for the next participant (Section 4.3).

8.1.1. Required PD Assessments with RHC

PVR, CO, PAP (mean), RAP (mean), RVP, hemoglobin, and MVO_2 will be measured via the RHC at the time points indicated in the SoA (Table 2). Oxygen consumption is part of the MVO_2 calculation and may be measured or estimated at 125 mL O_2 per square meter (m^2) of body surface area (BSA). These or other parameters may be optionally measured at other time points or omitted to ensure participant safety at the Investigator's discretion. If measurements are missed, or additional measurements are taken for safety purposes, the reason must be documented as an AE in the CRF.

Institutional procedures for insertion, care, monitoring, and removal of the RHC will be followed. Specific technique and procedures for measurement of PVR, CO, PAP, RAP, RVP, hemoglobin, oxygen consumption, and MVO_2 are provided in a separate Procedure Guide.

8.1.2. Required Non-invasive PD Assessments

Systemic blood pressure (mmHg) may be measured by inflatable cuff. Systemic blood pressure must include 3 values: systolic, diastolic, and mean arterial pressure. Arterial oxygen saturation (SpO_2, %) and heart rate (beats per minute) may be measured by pulse oximeter.

8.1.3. Nitric Oxide Challenge

NO challenge is to be performed after Baseline and before post-NO Baseline. Specific instructions for procedures and measurements are provided in a separate Procedure Guide.

8.1.4. Resting Respiratory Gas Exchange Assessments

Specific measurements for resting respiratory gas exchange assessment include changes from Baseline in respiratory rate (breaths per minute), minute ventilation (mL per minute), carbon dioxide production (VCO_2, mL per minute), end tidal oxygen concentration (ETO_2, %), and end tidal carbon dioxide concentration ($ETCO_2$, %). The gas exchange parameters will be monitored at the same time points as the PD assessments in Section 8.1.1 (Table 2, Table 4) with the exception of the 12 h assessment. Specific instructions for resting respiratory gas exchange assessment procedures and measurements are provided in a separate Procedure Guide.

8.1.5. Transthoracic Echocardiogram Assessments

Transthoracic echocardiogram is to be performed at Baseline and during a 2-8 hour window following TPIP administration (Table 4). Specific instructions for echocardiographic procedures and measurements are provided in a separate Procedure Guide.

8.1.6. Pulmonary CT Scan

8.1.6.1. Single-dose Period

Pulmonary CT scanning to assess pulmonary vasculature and blood flow is scheduled for Baseline and during a 4-8 hour window following TPIP administration (Table 4). Specific requirements and instructions for pulmonary CT scanning and required parameters are provided in a separate Procedure Guide.

8.1.6.2. Optional Extended Use Treatment Period

An optional pulmonary CT scan may be performed at first visit (±3 days) and at EUT Week 16 (±3 days) in the optional EUT period, as indicated in Table 6. The CT scan will be performed according to instructions provided by the CT scan vendor.

8.2. Safety Assessments

Evaluation of the safety and tolerability of single doses of TPIP in participants with PAH is the primary objective of this study. Planned time points for all safety assessments are provided in Table 1 and Table 2. The results of the individual participant's safety assessments during and after TPIP administration will contribute to the dosing decision for the next participant (Section 1.3.2). Participants who elect to enter the optional EUT period will also be monitored for safety, as listed in Table 6.

8.2.1. Physical Examinations

Screening: The physical examination must focus on those areas that determine the individual participant's eligibility to participate in the study and do so safely at the Investigator's discretion and will be documented accordingly.

Baseline: The physical examination must focus on the participant's fitness for the study procedures and TPIP administration.

Discharge: The physical examination must focus on the participant's fitness to be safely discharged to home from the inpatient setting. Special attention must be paid to assessment of any new or ongoing AEs.

Follow-up: The in-person physical examination must focus on participant safety and assessment of AEs that were ongoing at discharge or have occurred since discharge.

8.2.2. Vital Signs

8.2.2.1. Single-dose Period

Temperature, heart rate, respiratory rate, and blood pressure at screening and 48 hour post-TPIP administration follow-up will be per the Investigator's usual outpatient practice and documented accordingly.

Baseline and post-TPIP administration: Changes from Baseline in heart rate, respiratory rate, and systemic blood pressure are PD endpoints as well as safety variables and must be measured as specified (Section 8.1). Vital signs outside of PD endpoints will be monitored per the inpatient unit's usual practices.

8.2.2.2. Optional Extended Use Treatment Period

Changes in heart rate, respiratory rate, body temperature, and systemic blood pressure will be monitored as described in Table 6. Vital signs will be measured at Extended Use

Screening/Baseline (EUT Day 1), EUT Week 2, EUT Week 3, EUT Week 5, EUT Week 10, and EUT Week 16 and at the Early Discontinuation visit, if appropriate.

8.2.3. Electrocardiograms

Screening: a single 12-lead ECG will be conducted per the Investigator's usual practice

Baseline: A single 12-lead ECG will be performed to ensure the participant's eligibility for the study (Section 5.2). Inpatient telemetry monitoring will be utilized per the unit's usual practice until the participant is discharged from the inpatient setting, but routine telemetry readings will not be collected as study data unless they pertain to a relevant AE.

48 hours post-TPIP administration follow-up: a single 12-lead ECG will be conducted per the Investigator's usual practice.

8.2.4. Clinical Safety Laboratory Assessments

See Section 10.2 (Table 8) for the list of clinical laboratory tests to be performed and the SoA (Table 1, Table 2, Table 5, Table 6) for the timing and frequency. All clinical laboratory tests will be performed locally by the study site.

The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the Investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 7 days after TPIP dosing must be repeated at the Investigator's discretion, consistent with the participant's level of disease until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

- If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology must be identified, and Insmed notified.]
- All protocol-required laboratory tests, as defined in Section 10, Appendix 2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.4).
- If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose modification), then the results must be recorded.

8.2.5. Pregnancy Testing

8.2.5.1. Single-dose Period

Willingness of WOCBP to undergo serum or urine pregnancy testing is a study eligibility criterion. Pregnancy tests will be conducted at screening, baseline, and Study Day 30. WOCBP

participants will be provided a home pregnancy test kit with instructions to conduct and report test results at the Study Day 30 follow-up visit which is scheduled to be by telephone call or telemedicine. If the participant elects to enter the optional EUT period and the remote safety follow-up visit overlaps with the start of the EUT period, the results of a urine pregnancy test will be recorded at the first visit in the extended treatment period.

8.2.5.2. Optional Extended Use Treatment Period

Urine pregnancy tests will be performed in-clinic at EUT Baseline (EUT Day 1) in WOCBP. WOCBP participants will be provided home pregnancy test kits with instructions to conduct the pregnancy tests every 30 days or more if required during the treatment and follow-up periods. Study site personnel will contact the participant every 30 days by telephone and record the pregnancy test results. An additional on-site urine test must be performed prior to starting any procedure that requires the use of ionizing radiation.

8.3. Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

The definitions of AEs and SAEs can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative). AEs may be solicited or unsolicited. Solicited and unsolicited AEs are defined in Section 10.3.

The Investigator is responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE as provided in the protocol and remain responsible for following up all AEs.

The Investigator should proactively follow participants with AEs until the EOS for each participant. At the EOS visit, the Investigator will record the AE status (stable or not stable) in the electronic CRF.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs (serious and non-serious) for the core, single-dose period will be collected from the signing of the ICF until the Study Day 30 follow-up visit at the time points specified in the SoA (Table 1, Table 2). Medical occurrences that begin after obtaining informed consent but before TPIP administration will be recorded as Medical History/Current Medical Conditions, not as AEs.

SAEs that occur after signing the ICF but before study IMP starts must be recorded and reported as SAEs. Non-serious medical occurrences that begin after obtaining informed consent but before TPIP administration will be recorded as Medical History/Current Medical Conditions, not as AEs.

For participants who enroll in the EUT period, AEs for the period from the single-dose Study Day 30 follow-up until the enrollment in the EUT will be collected during participant's screening for the optional EUT period. All AEs and SAEs for participants who choose to enroll in the optional EUT period will be recorded at the time points specified in the SoA (Table 5, Table 6).

All SAEs will be recorded and reported to Insmed or designee immediately and under no circumstance must this exceed 24 hours, as indicated in Appendix 3, (Section 10.3). The Investigator will submit any updated SAE data to Insmed within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study IMP or study participation, the Investigator must promptly notify Insmed.

8.3.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. The Investigator should proactively follow participants with AEs until the EOS for each participant. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline due to study completion, then the site can report this information to the Medical Monitor by email or telephone.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to Insmed of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

Insmed has a legal responsibility to notify relevant health authorities and regulatory agencies about the safety of a study drug under clinical investigation. This study is being conducted in the USA only; regulatory requirements relating to safety reporting to the US FDA, IRBs, and investigators will be followed.

An Investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from Insmed will review and then file it along with other study documents and will notify the IRB, if appropriate according to local requirements.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Insmed policy and forwarded to Investigators as necessary. No serious adverse

reactions are considered expected for TPIP. Please refer to the Reference Safety Information in Section 6.1 of the Investigator's Brochure.

8.3.5. Pregnancy

Details of all pregnancies that occur in WOCBP participants within 30 days after TPIP administration will be collected. Male participants with WOCBP partners must continue to use contraception for 90 days after TPIP administration and report any pregnancies that occur within that time period.

If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to Insmed within 24 hours of learning of the pregnancy in a female participant or female partner of male participant and after obtaining the necessary signed informed consent from the female partner.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

Any female participant who becomes pregnant while participating in the study will be discontinued from the study.

8.3.6. Adverse Events of Special Interest (AESI)

There are no AESIs for TPIP that require special collection and rapid communication by the Investigator.

8.3.7. Medical Device Deficiencies

A medical device, the Plastiape capsule based Dry Powder Inhaler is being provided for use in this study to administer TPIP. To fulfill regulatory reporting obligations worldwide, the Investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a Medical Device deficiency and reporting requirements and procedures for device deficiencies and AEs/SAEs resulting from device deficiencies can be found in Section 10.6.

8.3.7.1. Time Period for Detecting Medical Device Deficiencies

- Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the Investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such a deficiency is considered reasonably related to a medical device provided for the study, the Investigator will promptly notify Insmed.

The method of documenting Medical Device Deficiency is provided in Section 10.6.

8.3.7.2. Follow-Up of Medical Device Deficiencies

Follow-up applies to all participants who experienced a device deficiency.

The Investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.

New or updated information will be recorded on the originally completed form with all changes signed and dated by the Investigator.

8.3.7.3. Prompt Reporting of Device Deficiencies to Insmed

Device deficiencies will be reported to Insmed within 24 hours after the Investigator determines that the event meets the protocol definition of a medical device deficiency.

8.3.7.4. Regulatory Reporting Requirements for Device Deficiencies

The Investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for Insmed to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The Investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB.

8.4. Pharmacokinetic Assessments

The schedule for PK assessments and sampling windows during the single-dose period is shown in Table 3. The 48 (± 4) hour post-TPIP administration blood draw is expected to be done on an outpatient basis.

8.4.1. PK Sample Collection

Plasma blood samples of approximately 10 mL each will be collected for measurement of plasma concentrations of TP and TRE as specified in the SoA (Section 1.4).

A maximum of 2 samples may be collected at additional time points during the study if an SAE occurs or at early termination.

Each PK plasma sample will be divided into 2 aliquots (1 each for PK analysis and the other for backup. All samples will be stored frozen (-70°C or -20°C) until shipment and then stored at -70°C until analysis. The actual date and time (24-hour clock time) of each sample will be recorded.

Full instructions for the collection and handling of PK samples will be provided by Insmed in a separate Laboratory Manual.

8.4.2. PK Analysis

Individual PK parameters of TRE and TP will be determined using non-compartmental analysis for the following parameters: C_{max}, t_{max}, $AUC_{t1–t2}$, $AUC_{0–\infty}$, CL/F, Vd/F, and $t_{1/2}$.

8.4.3. Pharmacokinetic and Pharmacodynamic Evaluations

Relationships between PK (TP dose and TRE exposure) and PD effects and safety will be explored and reported separately.

8.5. Genetics / Pharmacogenomics

Genetic and/or pharmacogenomic analyses are not included in this study.

8.6. Biomarkers

A blood sample for NT-pro-BNP will be taken at screening or Baseline if no historical value within 3 months of Baseline visit is available.

Blood samples (5-7 mL per time point) will be collected for biomarker measurement at Baseline and at 4 and 8 hours after TPIP administration. The plasma generated from the blood samples will be stored frozen (-70 C or lower is preferred) until shipment and analysis.

Full instructions for the collection and handling of biomarker samples will be provided by Insmed in a separate Laboratory Manual.

8.7. Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

8.8. Immunogenicity Assessments

Immunogenicity assessments do not apply to this study of a small molecule.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

No statistical hypotheses will be evaluated in this study.

9.2. Sample Size Determination

The sample size for this study is not based on statistical power calculations. The planned number of evaluable participants to complete the study is approximately 6-10.

9.3. Analysis Sets

The analysis sets comprise participants who are considered evaluable for the parameters under consideration.

All participants who receive a single dose of TPIP will be considered evaluable for safety and included in the safety population.

All participants who receive a single dose of TPIP and have a least one measurable post-dose plasma TP/TRE concentration will be considered evaluable for PK and included in the PK population.

All participants who receive a single dose of TPIP and have a Baseline datapoint and at least one measurable post-dose PD datapoint will be considered evaluable for PD and included in the PD population.

All participants who receive a single dose of TPIP and have at least 1 measurable post-dose biomarker datapoint will be considered evaluable for biomarkers and included in the biomarker population.

9.4. Statistical Analyses

The statistical analysis plan will be finalized prior to Database Lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

There is no hypothesis-testing in this study and no inferential statistical analyses will be conducted. There will be no proxy values for missing data. Participant PK, PD, and biomarker data will be presented individually in listings and graphs as appropriate for each variable.

The frequency of TEAEs is the primary endpoint for this study. All safety analyses will be performed on the safety population. AE listings as required by ICH E3 guidelines will be produced. TEAEs, SAEs, AEs leading to treatment and/or study withdrawal, and AESIs will be listed for each participant along with outcome, severity, and relatedness to study IMP. Ad hoc summaries of TEAEs may be prepared if the volume of data allow.

PK and PD values for secondary endpoints will be listed and graphed if appropriate for each evaluable participant.

PK and PD values for exploratory endpoints will be listed and graphed as appropriate for each participant.

9.4.2. ECG, Vital Signs, Clinical Laboratory Values

ECG data will be listed for each participant. Vital signs data that are not considered part of a PD assessment (Section 8.1) will be listed for each participant. Clinical laboratory values will be listed for each participant.

9.5. Interim Analysis

All available safety, PK, and PD data from each participant will be evaluated by the SRC prior to the next participant in order to determine the value of proceeding with the study and the TPIP dose for each subsequent participant (Section 4.3).

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

a. Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
b. Applicable ICH Good Clinical Practice (GCP) Guidelines
c. Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, Instructions for Use of the Plastiape capsule based Dry Powder Inhaler, and other relevant documents must be submitted to an IRB by the Investigator and reviewed and approved by the IRB before the study is initiated.

Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

d. Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
e. Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures
f. Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB, and all other applicable local regulations

10.1.2. Protocol Deviations

The Investigator must conduct the study in compliance with the protocol as agreed to by Insmed and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRB.

The Investigator must notify the IRB of deviations from the protocol in accordance with IRB reporting requirements.

As of May 2020, due to concern regarding COVID-19, there may be restrictions to participant attendance at in-clinic visits or elective inpatient admissions. In the event participants are restricted to attend in-clinic visits, or if the participant has concern regarding travel and attending in-clinic visits (due to potential public health concerns), the site must contact Insmed on how to

conduct the scheduled assessments, and decisions must be documented in the source documentation. Where necessary, in-clinic visits may be conducted via telemedicine link and home health care visits.

10.1.3. Public Health Emergency Situations

During the COVID-19 public health emergency, Insmed, IRBs, and Investigators shall follow the most current version of local guidance to assure the safety of study participants, maintain compliance with GCP, and minimize risks to study integrity. The continuity of clinical study conduct and oversight may require implementation of temporary or alternative mechanisms, which will remain in effect only for the duration of the local public health emergency. Examples of such mechanisms may include, but are not limited to, any of the following: telephone contact, virtual visits, telemedicine visits, online meetings, non-invasive remote monitoring devices, use of local clinic or laboratory locations, and home visits by skilled staff. The site must contact Insmed on how and when to implement temporary and/or alternative mechanism of scheduled assessments, and all decisions taken must be documented in the source documentation. Additionally, all temporary mechanisms utilized, and the resulting deviations from planned study procedures are to be documented as being related to COVID-19.

In a situation where local health authorities declare a public health emergency while the study is ongoing, the suggested guidance in the following subsections must be followed.

10.1.3.1. Continuation or Suspension of the Study

Ensuring the safety of trial participants is paramount. Insmed (Insmed Incorporated), in consultation with clinical Investigators and IRB, will determine if the protection of a participant's safety, welfare, and rights are best served by continuing or stopping the trial at the specific site. Such decision will depend on specific circumstances, including the ability to conduct appropriate safety monitoring, the potential impact on the investigational product supply chain, and other considerations.

If the decision is to continue the study, the following considerations will be taken into account:

10.1.3.1.1. Study Recruitment

Insmed will communicate to the sites the decision on whether to continue or suspend recruitment after considering the specific circumstances of each site, recommendation by the IRB, and its local health authority mandates. If, due to COVID-19, study discontinuation exceeds the assumed rate, Insmed may allow enrollment past the assumed sample size.

10.1.3.1.2. Participants Already Enrolled in the Study

If the decision is to continue the participation of participants already enrolled, the following steps must be taken:

- If a participant is not able to complete a protocol specified study visit, it may be necessary to adjust the visit schedule, convert in-clinic visits to telemedicine visits, and/or postpone study procedures until the next available in-clinic study visit. If there is information available from previous visits (e.g., laboratory assessments) that

requires follow-up procedures or other safety assessments, the Investigator will decide if an on-site visit or home healthcare visit is required or whether the participant's safety can be preserved by other means.

10.1.3.1.3. Participants Infected by COVID-19

If a participant has had a past documented mild to moderate COVID-19 infection prior to enrollment in the trial but the participant has recovered and the current diagnostic tests are negative (negative antigen by any diagnostic laboratory kit), the participant can be screened, at the Investigator's discretion. Participants who experienced hospitalization, severe disease, and/or COVID-19 acute respiratory distress syndrome (ARDS) must be excluded.

If a participant has a documented infection by COVID-19 while in the trial, the event will be reported as an AE or SAE, depending on the criteria. The Investigator will follow the guidance provided by health authorities in the treatment of those participants.

10.1.4. Financial Disclosure

The disclosed financial interest of the Investigator/sub-investigator must be collected before screening of the first participant, following study completion at the Investigator site and 1 year following overall study completion. The Investigator/sub-investigator must promptly update this information if any relevant changes occur during this period.

10.1.5. Informed Consent Process

Before a participant's participation in the study, it is the Investigator's responsibility to obtain freely given consent, in writing, from the participant or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any study IMPs are administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective participant, to the participant's participation in the clinical study. An informed consent document that includes both information about the study and the consent form will be prepared and given to the participant. This document will contain all the elements required by the ICH E6 (R2) Guideline for GCP and any additional elements required by local regulations. The written ICF must be prepared in the local language(s) of the potential participant population.

In obtaining and documenting informed consent, the Investigator must comply with the applicable regulatory requirements, and must adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form and any revision(s) must be approved by the IRB prior to being provided to potential participants.

The participant's written informed consent (written or electronic) must be obtained prior to his/her participation in the study, and must be documented in the participant's medical records, as required by applicable regulations. The ICF must be signed and personally dated by the participant or a legally acceptable representative, and by the person who conducted the informed consent discussion (not necessarily the Investigator). The signed ICF must be retained in accordance with institutional policy, and a copy of the signed consent form must be provided to

the participant or legal representative. The date and time that informed consent was given must be recorded in the CRF.
Participants who are rescreened are required to sign a new ICF.

10.1.6. Protection of Participant Identification and Confidentiality

The Investigators and Insmed will preserve the confidentiality of all participants taking part in the study, in accordance with GCP and local regulations.

The Investigator must ensure that the participant's anonymity is maintained. On the CRF or other documents submitted to Insmed, participants must be identified by a unique participant identifier as designated by Insmed. Documents that are not for submission to Insmed (e.g., signed ICFs) must be kept in strict confidence by the Investigator.

In compliance with ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB direct access to review the participant's original medical records for verification of study-related procedures and data. The Investigator is obligated to inform the participant that his/her study-related records will be reviewed by the above-named representatives without violating the confidentiality of the participant.

Participant names will not be supplied to Insmed. A participant number will be recorded in the CRF, and if the participant name appears on any other document (e.g., laboratory report), it must be obliterated on the copy of the document to be supplied to Insmed. All records will be kept confidential to the extent provided by federal, state, and local laws. The participants will be informed that representatives of Insmed, IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

The Investigator will maintain a personal participant identification list (participant numbers with the corresponding participant names) to enable records to be identified.

10.1.7. Committee Structure

An SRC will be responsible for monitoring safety data. The SRC will comprise all Investigators and key members of the Insmed Study Team (including but not limited to Medical Monitor, Medical Director(s), Safety/Pharmacovigilance Physician, Statistician, Clinical Pharmacologist) and external expert consultants. The SRC will continuously monitor all available safety, PD and PK data for each participant and will obtain consensus regarding the safety of continuing the study, the next TPIP dose, and clinical care of the next participant. Expert consultants may be invited to review and interpret participant data. With any safety findings, a decision will be made, based on the review, as to whether enrollment in the study will be allowed to continue. Decisions regarding final database values for PD parameters may be adjudicated by the SRC.

10.1.8. Dissemination of Clinical Study Data

Insmed will provide study information for inclusion in national registries according to national/local regulatory requirements.

Results of this study will be disclosed according to the relevant national regulatory requirements.

10.1.9. Data Quality Assurance

The Investigator/investigational site will permit study-related monitoring, audits, IRB review and regulatory inspections by providing direct access to source data/documents. Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of a clinical study.

10.1.9.1. Data Collection

All data obtained for this study will be entered into a 21 CFR Part 11 compliant Data Management System provided by Insmed or its designee. These data will be recorded with an EDC system using CRFs. The Investigator will ensure the accuracy and completeness of the data reported to Insmed. All data entry, modification or deletion will be recorded automatically in an electronic audit trail.

The Investigator will provide access to his/her original records to permit a representative from Insmed to verify the proper transcription of data. Data reported in the CRFs must be consistent with and substantiated by the participant's medical record and original source documents. The CRF data will be monitored by Insmed or designee. The final, completed CRF Casebook for each participant must be electronically signed and dated by the PI within the EDC system to signify that the Investigator has reviewed the CRF and certifies it to be complete and accurate.

Insmed will retain the final CRF data and audit trail. A copy of all completed CRFs will be provided to the Investigator.

10.1.9.2. Study Monitoring

Before study initiation, at a site initiation visit or at an Investigator's meeting, an Insmed representative will review the protocol, CRF, Investigator Brochure, and any study-related materials with the Investigators and their staff. During the study, Insmed study monitor or its designee will visit the site regularly to check the completeness of participant records, the accuracy of entries on the CRFs, adherence to the protocol, adherence to ICH GCP and applicable regulatory requirements, the progress of enrollment, and also to ensure that study IMP is being stored, dispensed, and accounted for according to specifications.

The Investigator must give the monitor access to relevant hospital or clinical records to confirm their consistency with the CRF entries. Participant confidentiality will be maintained by the study center. Insmed monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of primary activity and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study specific monitoring plan.

10.1.9.3. Audits and Inspections

Domestic and foreign regulatory authorities, the IRB, and an auditor authorized by Insmed may request access to all source documents, CRFs, and other study documentation for onsite audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must

provide support at all times for these activities. Medical records and other study documents may be copied during audit or inspection provided that participant names are obliterated on the copies to ensure confidentiality.

If an inspection is requested by a regulatory authority, the Investigator will inform Insmed, immediately that this request has been made.

10.1.9.4. Study Record Retention

Study documents must be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents must be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of Insmed. It is the responsibility of Insmed to inform the Investigator when these documents no longer need to be retained.

10.1.9.5. Source Documents

Source documentation is the point of initial recording of a piece of data. Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.10. Study Files and Materials

Before the start of any study related procedures, all initial documents required by ICH GCP, Good Pharmacoepidemiology Practice, and applicable local regulations must be available in the relevant files maintained by Insmed (or delegate) and the Investigator. An Investigator Study File prepared by Insmed (or delegate), containing all applicable documents for use at the study site, will be made available to the Investigator before the start of the study. A list of personnel and organizations responsible for conduct of the study as well as the list of Investigator-delegates (e.g., sub-investigator) at each site will be included in the Investigator Study File. The respective files will be kept and updated by Insmed (or delegate) and the Investigator, as applicable.

All study documentation and materials maintained in the Investigator Study File at the study site must be available for inspection by Insmed's study monitor (or delegate) to determine that all required documentation is present and correct.

The study may be audited by qualified delegates from Insmed or a competent regulatory authority.

10.1.11. Use of Stored Samples and Data

Clinical samples may be stored for 5 years or longer after completion of the study. The information already collected, including biological samples, will continue to be used to evaluate the study results and in future medical and pharmaceutical research activities. However, the stored samples will not be used for genetic evaluation unless stated in a separate consent document.

Stored samples will be labeled with study and participant information and secured with limited access and retained per protocol requirements and in accordance with the laboratory's operating procedures. Electronic data will be kept in password protected computers at the laboratory and then transferred to Insmed or CRO, as applicable, for data analysis. Samples and corresponding data will be tracked using the laboratory's specimen tracking system.

Prior Insmed and IRB approval are required before using or sharing study samples or data in ways not specifically specified in the study protocol during conduct of this study.

Any loss or unanticipated destruction of samples (e.g., freezer malfunction) or data (e.g., loss of a data sheet with individually identifiable information) that violates or compromises the scientific integrity of study data must be reported to Insmed and the IRB.

At any time, participants may inform the Investigator in writing that they do not wish to have their samples stored beyond the completion (termination) of the study. In this case, the Investigator will request that all known remaining samples be destroyed and report the disposition of samples to the requesting participants and the IRB.

10.1.12. Disposition of Stored Samples and Data

Participant samples will be secured with limited access and retained per protocol requirements and in accordance with the laboratory's operating procedures. Samples stored by the central laboratories will be labeled with the participant's study identification information. Data will be kept in password protected computers at the laboratory and then transferred to the vendor for data analysis. Samples and corresponding data acquired will be tracked using the laboratory's specimen tracking system.

In the future, if other Investigators may wish to study these samples and/or data, they need to obtain Insmed approval and participant consent before any sharing of samples and/or data.

Any loss or unanticipated destruction of samples (e.g., due to freezer malfunction) or data (e.g., loss of a data sheet with individually identifiable information) that results in a violation that compromises the scientific integrity of the data collected for the study will be reported to Insmed and the IRB.

Additionally, participants may withdraw authorization in writing to decline their sample storage for a period of up to 2 years beyond the duration of the study. In this case, the PI will request the destruction of all known remaining samples and report what was done to both the participant and to the IRB. This decision will not affect the individual's participation in the study.

10.1.13. Study and Site Start and Closure

Before the start of the study at each study site, Insmed's study monitor (or delegate) shall confirm adequacy of the facilities by study site visit or other acceptable methods.

The Investigator may not enroll any participant into the study before Insmed has received written approval or a favorable opinion from the IRB for conducting the study and a formal meeting has been conducted by Insmed's study monitor (or delegate) to initiate the study. This meeting will include a detailed review of the study plan, and completion of the CRF.

10.1.13.1. First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants. The first participant screened for participation in the study is considered the first act of recruitment.

10.1.13.2. Study/Site Termination

Insmed or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of Insmed. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by Insmed or Investigator may include but are not limited to:

For study termination:

- Discontinuation of further study IMP development

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB or local health authorities, Insmed's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, Insmed shall promptly inform the Investigators, the IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and must assure appropriate participant therapy and/or follow-up.

10.1.14. Protocol Amendments

Any substantial change or addition to this protocol requires a written protocol amendment that must be approved by Insmed, before implementation. Amendments significantly affecting the

safety of participants, the scope of the investigation, or the scientific quality of the study, require additional approval by the applicable regulatory authority(ies) and IRBs. Copies of the applicable written approvals must be filed in Insmed files and investigator site files.

The requirements for approval must in no way prevent any immediate action from being taken by the Investigator or by Insmed in the interests of preserving the safety of all participants included in the study. If an immediate change to the protocol is felt to be necessary by the Investigator and is implemented by him/her for safety reasons, Insmed or its agent must be notified and the applicable regulatory authority(ies)/IRBs must be informed as soon as possible. Any other regional reporting requirements must be adhered to.

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or regulatory authority/IRB approval, but the regulatory authority(ies)/IRBs must be kept informed of such administrative changes in accordance with country specific requirements.

10.1.15. Financing and Insurance

10.1.15.1. Finances

Prior to starting the study, the Investigator and/or institution will sign a clinical study agreement with Insmed. This agreement will include the financial information agreed upon by the parties.

10.1.15.2. Reimbursement, Indemnity, and Insurance

Reimbursement, indemnity, and insurance shall be addressed in a separate agreement on terms agreed upon by the parties.

10.1.15.3. Participant Reimbursement, Liability and Insurance

The civil liability of the involved parties with respect to financial loss due to personal injury and other damage that may arise as a result of this study being conducted are governed by the applicable legal requirement(s).

Insmed will provide insurance to the Investigator if required by the applicable regulatory and legal requirement(s).

If required by local law, participants taking part in this study will be insured against any injury caused by the study in accordance with the applicable regulatory and legal requirement(s).

10.1.16. Publication Policy

Any formal presentation or publication of data collected from this study will be considered as a joint publication by the Investigator(s) and the appropriate personnel of Insmed. Authorship will be determined by mutual agreement. For multi-center studies, it is mandatory that the first publication be based on data from all centers, analyzed as stipulated in the protocol by Insmed and statisticians, and not by the Investigators themselves. Investigators participating in multi center studies agree not to present data gathered from a single center or a small group of centers

before the full, initial publication, unless formally agreed to by all other Investigators and Insmed.

Insmed must receive copies of any intended communication in advance of publication (at least 15 working days for an abstract or oral presentation and 45 working days for a journal submission). Insmed will review the communications for accuracy (thus avoiding potential discrepancies with submissions to regulatory authorities), verify that confidential information is not being inadvertently divulged, and to provide any relevant supplementary information. Authorship of communications arising from pooled data may include members from each of the contributing centers as well as Insmed personnel.

At the conclusion of the study, after the data are analyzed, the results of study will be reported in a clinical study report.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 8 will be performed by the local laboratory. If local laboratory results are used to make a study IMP decision or response evaluation, the results must be recorded. Protocol-specific clinical laboratory requirements for the inclusion or exclusion of participants are detailed in Section 5.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 8: Protocol-Required Safety Laboratory Tests, INS1009-201

Category	Laboratory Parameters
Clinical Chemistry	Sodium, chloride, potassium, CO_2, magnesium, calcium, glucose, phosphate, total bilirubin (with direct and indirect fractionation, if total bilirubin is elevated >2 ULN), alkaline phosphatase, LDH, AST, ALT, CPK, albumin, total protein, creatinine, urea-nitrogen, uric acid, estimated glomerular filtration rate
Hematology	Hemoglobin, erythrocytes, hematocrit, MCH, MCV, MCHC, leukocytes, differential blood count of neutrophils, eosinophils, basophils, monocytes, lymphocytes, and platelets
Coagulation[a]	PT, PTT, INR
Serology[a]	HIV antibody, hepatitis B surface antigen [HBsAg], Hepatitis C virus antibody
Pregnancy test	Highly sensitive serum or urine hCG

[a] Not included in EUT screening for participants enrolling in the extended use treatment period.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; CO_2 = carbon dioxide; CPK = creatine phosphokinase; hCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; INR = international normalized ratio; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PT = prothrombin time; PTT = partial thromboplastin time; ULN = upper limit of normal

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

The definitions and procedures in this Appendix (Appendix 3) are for AEs and SAEs that do not involve the Plastiape capsule based Dry Powder Inhaler. For reporting device deficiencies or AEs involving the Plastiape capsule based Dry Powder Inhaler, please see Section 10.6.

10.3.1. Definition of AE

AE Definition
An AE is defined as any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, October 1994). A treatment emergent adverse event (TEAE) is defined as any AE that occurs after the first dose of study IMP and within 28 days after the last dose of study IMP

Events Meeting the AE Definition
Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), that worsen from Baseline, are considered clinically significant in the medical and scientific judgment of the Investigator (e.g., not related to progression of underlying disease), that are associated with signs and/or symptoms, require therapeutic intervention, or lead to discontinuation of the administration of study IMP must be reported as an AE Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. New conditions detected or diagnosed after study IMP administration even though it may have been present before the start of the study. Signs, symptoms, or the clinical sequelae of a suspected IMP- IMP interaction. Signs, symptoms, or the clinical sequelae of a suspected overdose of either study IMP or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses must be reported regardless of sequelae. The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. “Lack of efficacy” or “failure of expected pharmacological action” also constitutes an AE or SAE. Lack of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the PK and PD assessments.

Events NOT Meeting the AE Definition
Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Study INS1009-201 requires an overnight inpatient treatment period (Study Days 1-2). Complications that occur during the inpatient treatment period are AEs. If a complication prolongs the planned hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE must be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Is a suspected transmission of any infectious agent via an authorized medicinal product
g. Is an important medical event

h. Other situations:

Medical or scientific judgment must be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events must usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of IMP dependency or IMP abuse.

10.3.3. Recording and Follow-up of AE and/or SAE

AE and SAE Recording

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The Investigator will then record all relevant AE/SAE information.

It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to Insmed in lieu of completion of the completed AE reporting form.

There may be instances when copies of medical records for certain cases are requested by Insmed. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Insmed.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities.

Severe: An event that prevents normal everyday activities. An AE that is assessed as severe must not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

The Investigator is obligated to assess the relationship between study IMP and each occurrence of each AE/SAE.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
The Investigator will use clinical judgment to determine the relationship.
Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study IMP administration will be considered and investigated.
The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to Insmed. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Insmed.
The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Insmed to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide Insmed with a copy of any post-mortem findings including histopathology.
New or updated information will be recorded in the originally submitted documents.
The Investigator will submit any updated SAE data to Insmed within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

All SAEs, regardless of causality, must be reported to the organization delegated by Insmed on a Serious Adverse Event Report Form within 24 hours of becoming aware of the event; corrections and additions are required to be submitted within 24 hours. Study-specific email, phone, and fax number for SAE reporting information will be provided to the study sites.

Unexpected drug related SAEs as assessed by Insmed or authorized person qualify for expedited reporting and will be reported to the IRB, regulatory authorities, participating Investigators and, if cross reporting is required for SUSARs, in accordance with all applicable global laws and regulations. A SUSAR is a Serious Adverse Reaction, which is suspected to be caused by the investigational medicinal product and which is unexpected; e.g., its nature or severity is not

consistent with the information in the relevant Reference Safety Information. SAEs, including those that do not meet requirements for expedited reporting, and all other AEs will be reported to the regulatory agencies as appropriate (e.g., for the FDA these are reported in the Investigational New Drug annual report and for the European Medicines Agency, these are reported in the Development Safety Update Report).

SAE Reporting to Insmed via an Electronic Data Collection Tool
The primary mechanism for reporting an SAE to Insmed will be the electronic data collection tool. If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours. The site will enter the SAE data into the electronic system as soon as it becomes available. After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Medical Monitor by email or telephone.

SAE Reporting to Insmed via Paper Data Collection Tool
Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to Insmed. In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting time frames.

10.4. Appendix 4: Contraceptive and Barrier Guidance

Contraceptive use by men and women of childbearing potential (WOCBP) must be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Highly effective contraception methods include true abstinence (refraining from heterosexual intercourse during the study); combined (estrogen and progestogen containing) or progestogen only hormonal contraception associated with inhibition of ovulation and supplemented with a double barrier (preferably male condom); intrauterine devices; intrauterine hormone-releasing systems; or vasectomized partner.

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

INTRODUCTION

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a participant meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with Insmed clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug-Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

DEFINITIONS

Potential Hy's Law (PHL)

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3×ULN and total bilirubin (TBL) ≥2×ULN at any point during the study irrespective of an increase in alkaline phosphatase (ALP). The elevations do not have to occur at the same time or within a specified time frame.

Hy's Law (HL)

AST or ALT ≥3× ULN and TBL ≥2×ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug. The elevations do not have to occur at the same time or within a specified time frame.

IDENTIFICATION OF POTENTIAL HY'S LAW CASES

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

1. ALT ≥ 3xULN
2. AST ≥ 3xULN
3. TBL ≥ 2xULN

The Investigator will review without delay each new laboratory report and if the identification criteria are met will:

1. Notify Insmed representative
2. Determine whether the participant meets PHL criteria (see DEFINITIONS of this Appendix) by reviewing laboratory reports from all previous visits

3. Promptly enter the laboratory data into the laboratory CRF

FOLLOW-UP

POTENTIAL HY'S LAW CRITERIA NOT MET

1. If the participant does not meet PHL criteria the Investigator will:
2. Inform Insmed representative that the participant has not met PHL criteria.
3. Perform follow-up on subsequent laboratory results according to the guidance provided in the clinical study protocol

POTENTIAL HY'S LAW CRITERIA MET

If the participant does meet PHL criteria the Investigator will:

- Notify Insmed representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or Baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician
- Complete the 3 Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

The instructions in this section must be followed for all cases where PHL criteria were met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than drug-induced liver injury caused by the IMP. The Insmed Medical Science Director and Global Safety Physician will also be involved in this review together with other participant matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

- If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE
- If the alternative explanation is not an AE, record the alternative explanation on the appropriate CRF

If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow Insmed standard processes.

If it is agreed that there is no explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to Insmed standard processes.
- The 'Medically Important' serious criterion must be used if no other serious criteria apply
- As there is no alternative explanation for the HL case, a causality assessment of 'related' must be assigned.

If there is an unavoidable delay, of over 3 weeks in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

10.6. Appendix 6 Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

The definitions and procedures detailed in this appendix are in accordance with ISO 14155.

Both the Investigator and Insmed will comply with all local reporting requirements for medical devices.

The detection and documentation procedures described in this protocol apply to all Insmed medical devices provided for use in the study. See Section 6.1.3 for the list of Insmed medical devices.

10.6.1. Definition of Medical Device AE and ADE

Medical Device AE and ADE Definition
An AE is any untoward medical occurrence in a clinical study participant, users, or other persons, temporally associated with the use of study IMP, whether or not considered related to the investigational medical device. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved. An adverse device effect (ADE) is defined as an AE related to the use of an investigational medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.6.2. Definition of Medical Device SAE, SADE and USADE

A Medical Device SAE is an any serious adverse event that:
a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in: A life-threatening illness or injury. The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death if it were more severe. A permanent impairment of a body structure or a body function. Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function. Chronic disease (MDR 2017/745).
c. Led to fetal distress, fetal death, or a congenital abnormality or birth defect

d. Is a suspected transmission of any infectious agent via a medicinal product
SADE definition
A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of an SAE. Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.
Unanticipated SADE (USADE) definition
An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is defined as a serious adverse device effect that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report (Section 2.3).

10.6.3. Definition of Device Deficiency

Device Deficiency Definition
A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and information supplied by the manufacturer.

10.6.4. Recording and Follow-up of AE and/or SAE and Device Deficiencies

AE, SAE, and Device Deficiency Recording
When an AE/SAE/device deficiency occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. The Investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the Investigator's normal clinical practice and on the appropriate form. It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to Insmed in lieu of completion of the AE/SAE/device deficiency form. There may be instances when copies of medical records for certain cases are requested by Insmed. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Insmed. The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. For device deficiencies, it is very important that the Investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency. A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE/SAE/device deficiency reported during the study and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe must not be confused with an SAE. "Severe" is a category used for rating the intensity of an event; both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, **not** when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study IMP and each occurrence of each AE/SAE/device deficiency.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship, cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study IMP administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure and/or Instructions for Use of the device in his/her assessment.
- For each AE/SAE/device deficiency, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/device deficiency and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to Insmed. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Insmed.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE/SAE/device deficiency

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Insmed to elucidate the nature and/or causality of the AE/SAE/device deficiency as fully as

possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide Insmed with a copy of any post-mortem findings including histopathology.
New or updated information will be recorded in the originally completed form.
The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.6.5. Reporting of SAEs

SAE Reporting to Insmed via an Electronic Data Collection Tool

The primary mechanism for reporting an SAE to Insmed will be the electronic data collection tool.
If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next table) to report the event within 24 hours.
The site will enter the SAE data into the electronic system as soon as it becomes available.
After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next table) or to the Medical Monitor by telephone.

SAE Reporting to Insmed via Paper Data Collection Tool

Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to Insmed.
In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE paper data collection tool sent by overnight mail or courier service.
Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE paper data collection tool within the designated reporting time frames.

10.6.6. Reporting of SADEs

SADE Reporting to Insmed

NOTE: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

Any device deficiency that is associated with an SAE must be reported to Insmed within 24 hours after the Investigator determines that the event meets the definition of a device deficiency.

Insmed will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs as required by national regulations.

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Signature Page for INS1009-201 Protocol Amendment No. 2

Approve	[redacted] 03-Mar-2022 20:29:08 GMT+0000

CLINICAL STUDY PROTOCOL

An Open-Label Study to Assess the Safety, Pharmacokinetics, and Pharmacodynamics of Treprostinil Palmitil Inhalation Powder in Participants with Pulmonary Arterial Hypertension

Protocol Number: INS1009-201

Version Number: 3.0

Amendment Number: 2

Compound: Treprostinil Palmitil Inhalation Powder (TPIP)

Study Phase: 2a

Sponsor Name: Insmed Incorporated

Legal Registered Address:
700 US Highway 202/206
Bridgewater, NJ 08807-1704
USA

Regulatory Agency Identifier Number(s)
IND: 147264
EudraCT: 2022-000839-23

Date: 03 MAR 2022

IMPORTANT CONTACTS

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ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ALT	alanine amino transferase
AST	aspartate amino transferase
AUC	area under the concentration-time curve
$AUC_{0-\infty}$	area under the concentration-time curve from time zero to infinity
AUC_{t1-t2}	area under the plasma concentration-time curve from time zero to time of last measurable concentration
CL/F	apparent total clearance of drug from plasma after extravascular administration
C_{max}	maximum (peak) plasma concentration of the drug
CO	cardiac output
CRF	case report form
CRO	contract research organization
CT	computerized tomography
DILI	drug induced liver injury
DPI	dry powder inhalation
ECG	electrocardiogram
EDC	electronic data capture
EOS	end of study
EUT	extended use treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice

HIV	Human Immunodeficiency Virus
HL	Hy's Law
ICF	informed consent form
ICH	International Council for Harmonisation
ICU	intensive care unit
IMP	investigational medicinal product
IRB	investigational review board
IV	intravenous
MAD	multiple ascending dose
mPAP	mean pulmonary arterial pressure
MVO_2	mixed venous oxygen saturation
NOAEL	No observed adverse effect level
NT-pro-BNP	N-terminal (NT)-pro hormone brain natriuretic peptide
PAH	pulmonary arterial hypertension
PAP	pulmonary arterial pressure
PD	pharmacodynamic(s)
PH	pulmonary hypertension
PHL	potential Hy's Law
PI	principal investigator
PK	pharmacokinetic(s)
PVR	pulmonary vascular resistance
QD	Once daily
QID	four times daily
RAP	right atrial pressure

RHC	right heart catheter
RVP	right ventricular pressure
SAD	single ascending dose
SAE	serious adverse event
SARS CoV 2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
SoA	schedule of activities/assessments
SUSAR	suspected unexpected serious adverse reaction
SRC	Safety Review Committee
$t_{1/2}$	elimination half-life
TBL	total bilirubin
TAPSE	tricuspid annular plane systolic excursion
TEAE	treatment emergent adverse event
t_{max}	time to maximum (peak) plasma concentration following drug administration
TPIP	treprostinil palmitil inhalation powder
TPIS	treprostinil palmitil inhalation suspension
TRE	treprostinil
TP	treprostinil palmitil
TVR	tricuspid valve regurgitation
ULN	upper limit of normal
US	United States
VCO_2	carbon dioxide production
Vd/F	apparent volume of distribution at terminal phase

WHO	World Health Organization
WOCBP	woman of child-bearing potential

1. PROTOCOL SUMMARY

1.1. Protocol Amendment Summary of Changes

Amendment 2 (03 MAR 2022)

This amendment is considered to be substantial.

Overall Rationale for the Amendment:

The primary driver for the changes in the protocol amendment is to account for the proper drug product availability and to incorporate the 80 µg formulation earlier in the dosing schema.

Grammatical and typographical errors were corrected throughout the document.

A summary of major changes in this amendment, compared to the original protocol, is shown in the table below.

Revision	Rationale	Location of Revision
Updated description of first dose to include the 80 µg formulation	To account for the proper drug product availability	• Section 1.3.2.1 • Section 4.1 • Section 4.3.1 • Section 6.1.1
Updated Inclusion Criterion #2	To eliminate the time constraint on right heart catherization history	• Section 5.1
Updated Inclusion Criterion #10	To reduce the required BMI from “19.0” to “18.0”	• Section 5.1
Updated Schedule of Assessments	To include 12-lead ECG, Inclusion/Exclusion criteria, targeted physical examination, and study drug accountability	• Table 6
Included “bleeding” as a risk with TRE	To be complete in the list of example effects of TRE on prostanoid metabolism	• Section 2.2

Document History		
Document	**Version**	**Date**
Global Amendment 2	3.0	03 MAR 2022
Global Amendment 1	2.0	06 OCT 2021
Original Protocol	1.0	02 NOV 2020

1.2. Synopsis

Protocol Title:

An Open-Label Study to Assess the Safety, Pharmacokinetics, and Pharmacodynamics of Treprostinil Palmitil Inhalation Powder in Participants with Pulmonary Arterial Hypertension

Rationale:

Treprostinil palmitil (TP) is an inactive prodrug of treprostinil (TRE), which is widely used in the treatment of pulmonary hypertension (PH). Treprostinil palmitil inhalation powder (TPIP) is a dry powder for inhalation formulation of TP. TPIP is being developed for the treatment of pulmonary arterial hypertension (PAH; World Health Organization (WHO) Group 1 PH). TPIP is expected to provide extended release of TRE in the lung with the goals of less frequent and more convenient and consistent dosing while reducing the frequency and severity of dose-limiting side effects associated with the currently approved forms of TRE. No studies of TP or TPIP have been conducted in participants with PAH. The purpose of this study is to evaluate the safety, pharmacokinetics (PK), and pharmacodynamic (PD) effects of a single dose of TPIP in participants with PAH.

The starting and planned doses for this study are primarily based on the safety and tolerability of treprostinil palmitil inhalation suspension (TPIS) in healthy participants following single inhalation at 85 to 340 µg (Study INS1009-101) and TPIP in healthy participants in a SAD/MAD study (Study INS1009-102). In INS1009-101, the systemic exposure for TRE at 340 µg was low (AUC < 2.5 ng*h/mL) with an elimination $t_{1/2}$ of approximately 7 hours. In rats, the PK profile of TP inhalation solution was similar to that of TP inhalation powder. In INS1009-102, single doses of up to 675 µg and multiple doses of up to 225 µg for 7 days were administered to healthy participants. Overall, TP was well tolerated, with largely mild TEAEs and an adverse effect profile consistent with that of inhaled prostacyclin analogs. Treprostinil exposures increased approximately dose-proportionately, were similar between TPIS and TPIP, and showed no accumulation with once daily (QD) dosing.

Objectives and Endpoints:

Objectives	Endpoints
Primary	Primary

• To evaluate the safety and tolerability of single doses of TPIP in participants with PAH	• Frequency of TEAEs
Secondary	Secondary
• To evaluate the PD effects of single doses of TPIP on PVR in participants with PAH over the first 24 hours following administration	• Change from Baseline in PVR at 8 and 24 hours after TPIP administration
• To evaluate the PK of TPIP as TRE in participants with PAH	• C_{max}, t_{max}, $AUC_{t1–t2}$, $AUC_{0–\infty}$, $t_{1/2}$ of TRE in plasma

TPIP=treprostinil palmitil inhalation powder; PAH=pulmonary arterial hypertension; TEAE=treatment emergent adverse event; PD=pharmacodynamic; PVR=pulmonary vascular resistance; PK=pharmacokinetics; TP=treprostinil palmitil; TRE=treprostinil; C_{max}=maximum observed concentration; t_{max}=time to maximum concentration after drug administration; $AUC_{t1–t2}$= area under the concentration time curve from time zero to last sampling time point with measurable concentration; $AUC_{0–\infty}$=area under the concentration time curve from time zero to infinity; $t_{1/2}$=elimination half-life

Overall Design:

This is a Phase 2a open-label study to assess the safety, tolerability, PD effects, and PK of TPIP administered to participants with PAH. This is the first study of TPIP in participants with PAH. Each participant will receive a single dose of TPIP, which may vary from participant to participant, as determined by the Safety Review Committee (SRC) for the study. The study includes a 24-hour inpatient observation period following TPIP dosing, during which PK, PD, and safety parameters will be assessed. An optional extended treatment period of 16 weeks will be available to participants who have completed the single-dose inpatient treatment period. When available, participants may be eligible to enroll in a separate open-label extension study (OLE) study that will have a duration of approximately 2 years. Details of the planned OLE study will be provided in a separate protocol. The study is designed to ensure the safety of and maintain minimal risk to participants. The cardiopulmonary and overall functional status of participants with PAH can be labile and medical instability can develop quickly. As such, there is considerable flexibility built into the protocol to allow Investigator discretion with the frequency, timing, and/or conduct of PD and PK assessments to again ensure participants' safety.

Brief Summary:

The study is designed to investigate the safety and acute pharmacokinetic (PK) and pharmacodynamic (PD) effects of a single dose of treprostinil palmitil inhalation powder (TPIP) in participants with pulmonary arterial hypertension (PAH). Intensive monitoring of pulmonary vascular resistance, cardiac output, right ventricular pressure, pulmonary arterial pressure, hemoglobin, right atrial pressure, and mixed venous oxygen saturation via right heart catheter in an appropriate inpatient setting is essential to understand how TPIP affects cardiopulmonary

hemodynamics and to elucidate dose- and PK-effect relationships. Some assessments and study activities (resting respiratory gas exchange assessment, transthoracic echocardiogram, pulmonary computerized tomography scan) for exploratory endpoints are optionally left to the discretion of the individual Investigator, based on participant safety and study site capabilities.

For individual participants, the study will consist of an outpatient screening period lasting up to 30 days. The inpatient treatment period will start on Study Day 1 and is expected to last overnight into Study Day 2. Outpatient PK sampling and safety follow-up at 48 hours post TPIP dose will extend into Study Day 3. A remote safety follow-up visit (telephone visit) is scheduled for Study Day 30 (± 2 days). An optional extended treatment period of 16 weeks will be available to participants who have completed the single-dose inpatient treatment period. There will be a second safety follow-up visit 30 days (± 3 days) after extended use treatment (EUT) Week 16 for participants who elect to enter the extended use treatment period. If the initial remote safety follow-up visit overlaps with the start of the extended treatment period, the initial remote safety visit will be shortened and conducted just prior to administration of IMP in the extended treatment period.

Number of Participants:

Approximately 6 to 10 evaluable participants are planned. Evaluable participants for safety are those who receive a single dose of TPIP; evaluable participants for PD and PK endpoints are those who receive a single dose of TPIP and have at least 1 post-TPIP administration PK or PD datapoint.

Treatment Groups and Duration:
This is a multi-center, open-label, non-randomized study. There are no predefined treatment groups. The dose determination for each participant will be made based on all available PK, PD, and safety data at the time of the participant's entry into the study. An optional extended use treatment period of 16 weeks will be available to all participants.

Safety Review Committee:
A Safety Review Committee (SRC) will be responsible for monitoring safety data. The SRC will comprise all Investigators and key members of the Insmed Study Team (including but not limited to Medical Monitor, Medical Director(s), Safety/Pharmacovigilance Physician, Statistician, Clinical Pharmacologist) and external expert consultants. The SRC will continuously monitor all available safety, PD and PK data for each participant and will obtain consensus regarding the safety of continuing the study, the next TPIP dose, and clinical care of the next participant. Expert consultants may be invited to review and interpret participant data. With any safety findings, a decision will be made, based on the review, as to whether enrollment in the study will be allowed to continue. Decisions regarding final database values for PD parameters may be adjudicated by the SRC.

1.3. Schema

1.3.1. Participant Progression Through the Study

The main study comprises an outpatient screening period, an inpatient treatment period, and an outpatient follow-up period. Participant progression through the study is shown in Figure 1. An optional EUT period is shown in Figure 2.

1.3.1.1. Screening Period

The outpatient screening period will last up to 30 days. After participants complete screening and have met the study eligibility criteria, the right heart catheter (RHC) procedure and inpatient treatment period should be scheduled without delay.

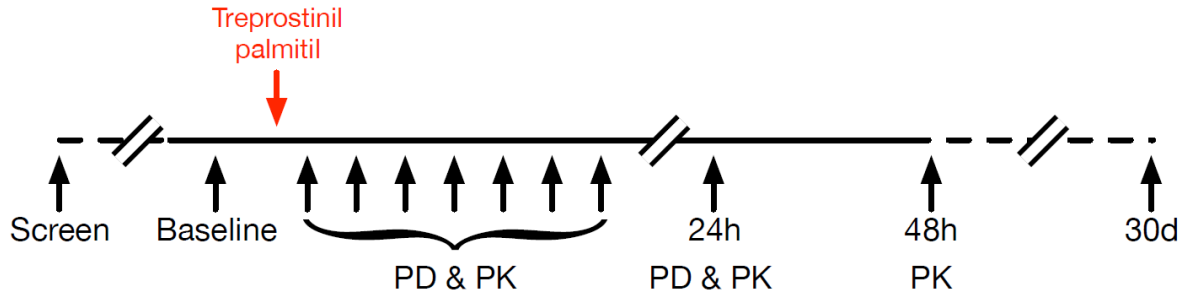
1.3.1.2. Inpatient Treatment Period

The inpatient treatment period will start on Study Day 1 and extend overnight into Study Day 2. Because the study requires an inpatient treatment period, institutional requirements for elective inpatient admissions, which may vary from site to site, will be followed. The participant may be required to undergo pre-admission assessments required by the institution for elective admission, for example testing for common infectious pathogens. Signature of elective admission documents and other consents may be required by the institution. An RHC will be placed. Following completion of Baseline assessments, a single dose of TPIP will be administered via a dry powder inhaler. Safety, PD, and PK assessments will continue at scheduled intervals through 24 hours following TPIP administration. Following the final assessments at 24 hours, the RHC will be removed and the participant will be discharged from the inpatient setting when deemed safe for the participant.

1.3.1.3. Follow-up Period

PK blood draw at 48 (± 4) hours after TPIP dosing will be done on an outpatient basis as arranged by the site. The 48-hour post-TPIP visit will also include safety assessments including physical examination, clinical laboratory evaluations, ECG, AE collection and vital signs. An additional safety follow-up will be conducted by telephone call or telemedicine on Study Day 30 (± 2 days) unless the participant elects to enter the EUT period prior to this follow-up visit. If the initial remote safety follow-up visit overlaps with the start of the extended treatment period, the initial remote safety visit will be shortened and conducted just prior to administration of investigational medicinal product (IMP) in the extended treatment period.

Figure 1: Participant Progression Through INS1009-201 Study[a]



PD-pharmacodynamic assessments; PK=pharmacokinetic assessments; h=hours; d=days
[a] Does not include optional extended use treatment period; the 30 day follow-up visit will be shortened and conducted just prior to administration of IMP in the extended treatment period if the visit overlaps with the start of the extended treatment period.

1.3.1.4. Optional Extended Use Treatment Period

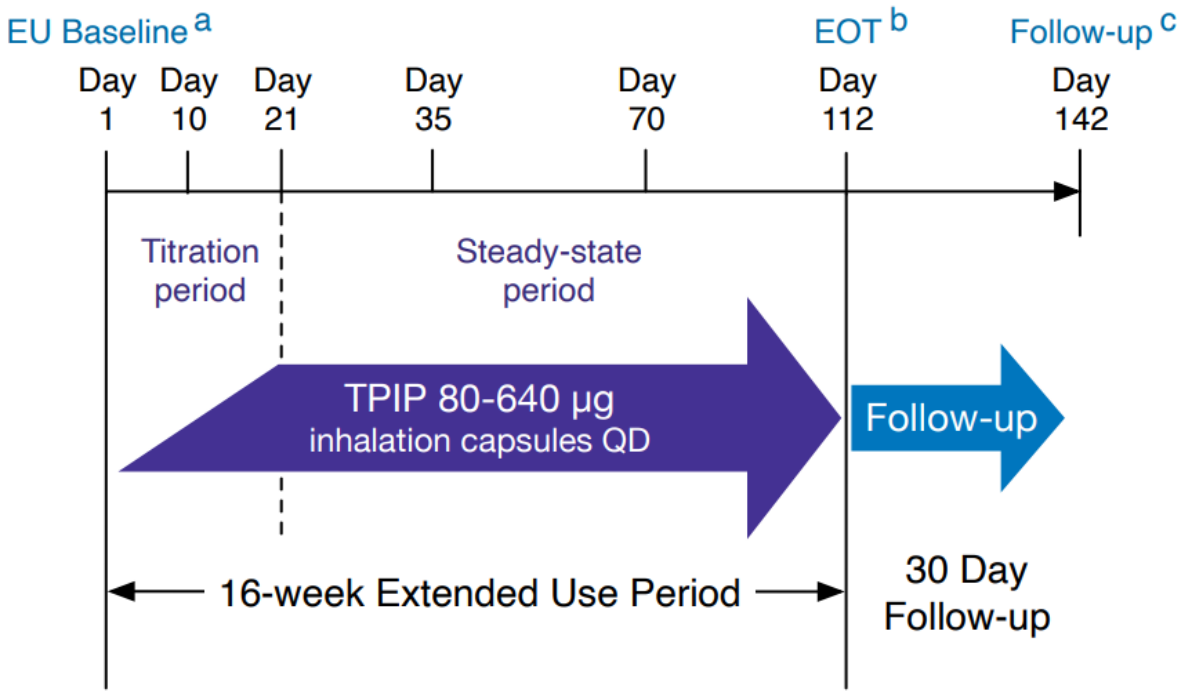
All participants will be allowed to enter the optional 16 week EUT period after the completion of the inpatient treatment period and final PK sample collection. Entry into the optional EUT period will be at participant and Investigator discretion. A gap between the inpatient treatment period and EUT period is expected, but not required, and can be up to 6 months.

After collection of the final PK sample, all participants will be allowed optional continued access to IMP for 16 weeks (includes a 3-week titration period) from first administration in the EUT period. At the Investigator's discretion, participants may undergo a study drug taper for up to 2 weeks after the Week 16 visit to help facilitate a safe withdrawal from study drug.

Participants will be screened to ensure they meet inclusion and exclusion criteria if they enter the EUT period more than 30 days after beginning the single-dose period (e.g., beyond the initial 30 day follow-up period) (Table 5).

Participant in-clinic study visits will be scheduled for EUT at Baseline (EUT Day 1), EUT Week 2, EUT Week 3, EUT Week 5, EUT Week 10, and EUT Week 16.

Figure 2: Participant Progression Through the Optional Extended Use Treatment Period



[a] The 30 day follow-up visit from the single dose period will occur on EU Day 1 if the visit overlaps with the start of the extended treatment period.
[b] At the Investigator's discretion, participants may undergo a study drug taper for up to 2 weeks after the Week 16 visit.
[c] The follow-up telephone call or visit will be 30 days after the Week 16 visit.
EU = Extended Use; QD = once daily; EOT = end of treatment

1.3.1.5. Extended Use Follow-up Period

There will be a second remote safety follow-up visit 30 days (± 3 days) after EUT Week 16 administration for participants who elect to enter the EUT period.

1.3.2. Dose Selection

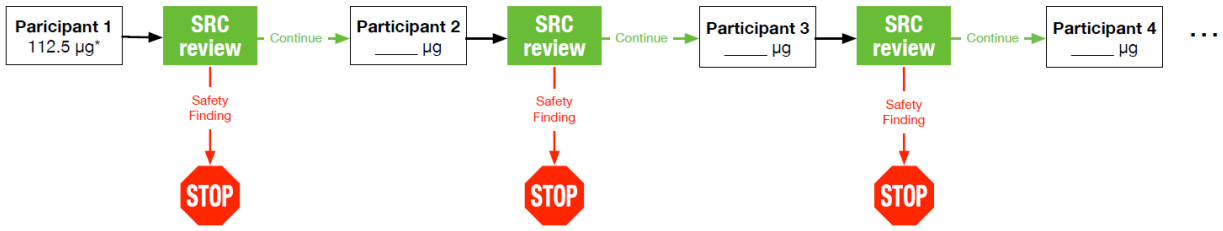
1.3.2.1. Inpatient Treatment Period Dose Selection

Each participant will enter the study in a serial fashion, following review of available safety, PK, and PD data from all previous participants by the Safety Review Committee (SRC). Each participant will receive a single-dose administration of TPIP via a dry powder inhaler. TPIP will be administered to only one participant at a time, with full evaluation of all available data prior to dosing the next participant.

The first participant should receive a dose of TPIP containing 112.5 µg; if the 112.5 µg formulation is not available due to expiration date, it is acceptable to use the 80 µg formulation.

The SRC will then review all available safety, PD, and PK data including data from the first participant and select the TPIP dose and any changes to the assessments for the second participant. Then, following review of all available data including that from the first and second participants, the SRC will select the dose for the third participant. Similarly, all available data from previous studies and participants will be assessed prior to determining the dose for the next participant, until such a time as the SRC believes the study must conclude. Figure 3 describes the planned dose-selection and study continuation process.

Figure 3: Schematic of Study Continuation Planning after Participant 1, INS1009-201



*80 µg following expiry of 112.5 µg formulation

SRC=Safety Review Committee

1.3.2.2. Optional Extended Use Treatment Period

Entrance into the optional EUT period is at participants' and Investigators' discretion and begins with a titration. The guideline for the optimal 3-week planned titration schedule is provided in Figure 4. The target TPIP dose will be achieved with a combination of dry powder capsules containing 80 µg, 160 µg, and 320 µg of TP.

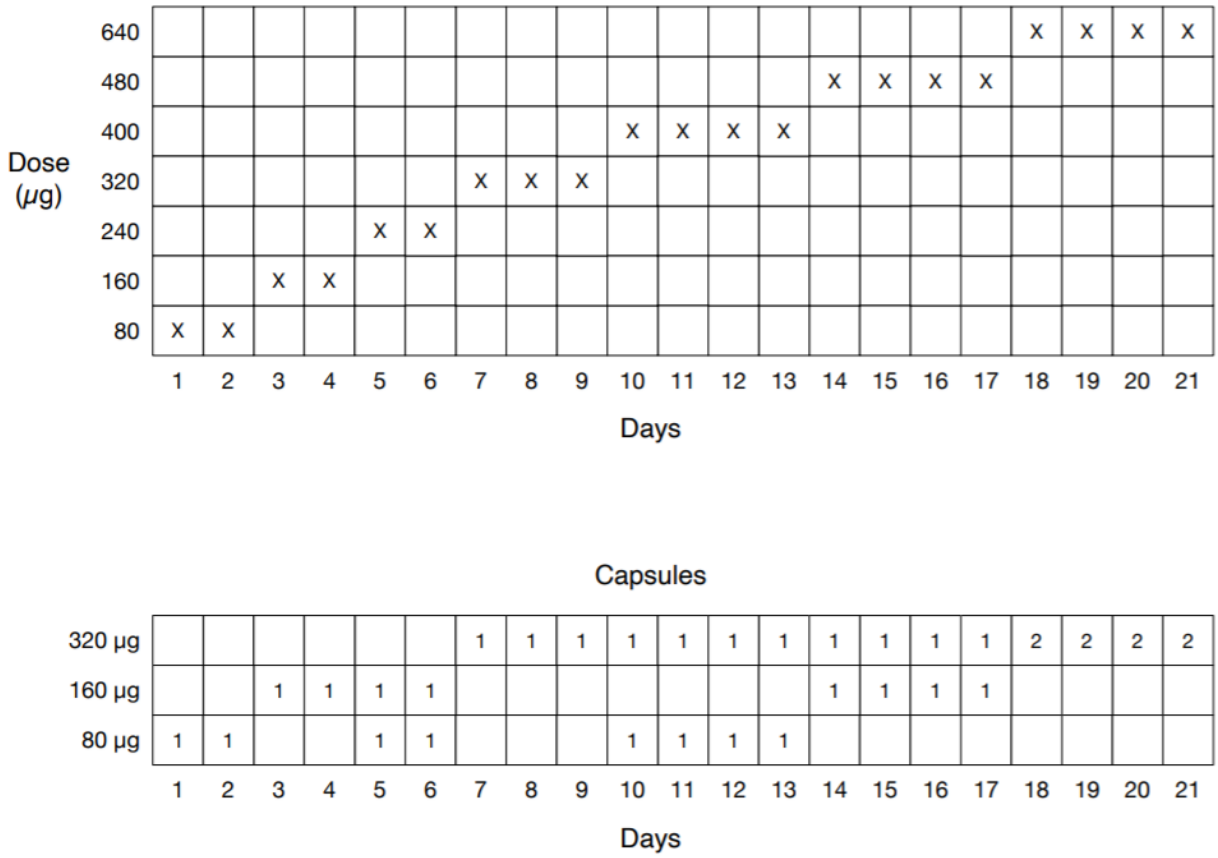
During the titration period (EUT Days 1 to 21), each participant's dose will be up-titrated to the highest tolerated dose for that individual. Participants will start open-label study drug with 1 capsule (80 µg TPIP) QD. If this dose is well tolerated, the dose should be up-titrated until reaching the participant's highest tolerable dose as described by the dosing schedule in Figure 4. During this titration period, participants must stay on study drug for the minimum number of cumulative days required for each dose (e.g., 2 days at 80 µg, 160 µg, or 240 µg; 3 days at 320 µg; or 4 days at 400 µg or 480 µg) prior to titrating to the next higher dose. Study drug titration may occur slower, but not faster, than described in Figure 4. If a dose is not tolerated, study drug may be decreased to the previous dose level. At the Investigator's discretion, up-titration may resume (as described in Figure 4) until the participant's highest tolerated dose is achieved at EUT Day 21.

All dose adjustments must be preceded by contact with the Investigator or study site personnel. In addition, the Investigator and/or study site personnel will be in contact with participants during the dose adjustment period to assess the tolerability to study drug as measured by the AEs commonly observed with other prostacyclin receptor agonists, which include headache, flushing, nausea, cough, and muscle pain. The decision to up-titrate to the next TPIP dose will be based on safety and tolerance data (e.g., AEs) as reported by the participant and assessed by the Investigator.

At the Investigator's discretion, based on tolerability, the study drug dose may be increased by 1 dose level (as described in Figure 4) at the EUT Week 5 in-clinic visit for participants who have not achieved the 640 µg dose. The increase in dose will be administered under clinical observation at the study site to ensure tolerability and correct dosing and self-administration of study drug. The participant's highest dose tolerated is expected to continue for the remainder of the study after the EUT Week 5 visit.

At the Investigator's discretion, participants may undergo a study drug taper for up to 2 weeks after the EUT Week 16 visit to help facilitate a safe withdrawal from study drug. The Investigator and/or study site personnel will be in contact with participants during the study drug taper to assess the tolerability to study drug.

Figure 4: Guideline for Optimal 3-Week Planned Titration Schedule (Optional Extended Use Treatment Period)



1.4. Schedule of Activities (SoA)

The SoA is divided into the following tables:

- Screening and follow-up activities in the single-dose period
- SoA in the inpatient treatment period
- PK and PD biomarker blood sampling schedule
- Optional procedures and assessments in the inpatient treatment period
- Screening and follow-up activities in the EUT period
- SoA in the EUT period

The single-dose period refers to the combination of the inpatient treatment period (Study Day 1 to Study Day 2), the PK/PD sampling period, and the 30 day follow-up period.

Table 1: Schedule of Activities for Screening and Follow up, Single-Dose Period, INS1009-201

Procedure	Screening	Follow-up	
	Up to 30 Days	48 h post TPIP dose[a]	Study Day 30 (± 2 days)[b]
Informed Consent	X	--	--
Inclusion/Exclusion Criteria	X	--	--
Demographics and Medical History	X	--	--
Smoking Status	X	--	--
Height, Weight, BMI Calculation	X	--	--
Prior/Concomitant Medications	X	X	X
Serology (HBsAg, HIV antibody, HCV antibody)	X	--	--
Serum Pregnancy Test (WOCBP only)	X	—	—
Urine Pregnancy Test (WOCBP only)	--	—	X
Hematology, Clinical Chemistry (Table 7)	X	X	--
Coagulation Profile (Table 7)	X	--	--
NT-pro-BNP Sample (if needed, Section 5.1)	X	--	--
12-lead ECG	X	X	--
Physical Examination	X	X	--
Vital Signs	X	X	--
6 Minute Walking Distance Test (if needed, Section 5.1)	X	--	--
Pulmonary Function Testing (if needed, (Section 5.1)	X	--	--
Adverse Events[c]	X	X	X

[a] 48 h safety follow-up assessments are to be conducted at the time of the visit for the 48h PK blood draw (Table 3).
[b] Follow-up visit will be shortened and conducted just prior to administration of IMP in the extended treatment period if the visit overlaps with the start of the extended treatment period.
[c] AE collection is from the time of signing the informed consent through the Day 30 safety follow-up. Events between ICF signing and TPIP dosing that are serious will be recorded as SAE; non-serious events during this period must be recorded as medical history.
Note: Additional safety follow-ups may be conducted at any time per the investigator's discretion to ensure participant safety. The reason for any additional safety follow-up must be reported as an AE.
BMI = body mass index; ECG = electrocardiogram WOCBP = woman of childbearing potential

Table 2: Schedule of Activities for Inpatient Treatment Period, INS1009-201

Treatment Period (Study Day 1 to Study Day 2)											
	Pre-TPIP Administration	**TPIP Administration**	**Post-TPIP Administration**								
Procedure	Day 1 Baseline	Time 0	30 min	60 min	90 min	2 h	3 h	4 h	8 h	24 h	24 h to discharge
Hematology, clinical chemistry, coagulation profile blood draw[a]	X	--	--	--	--	--	--	--	--	X	--
Urine pregnancy test (WOCBP only)	X	--	--	--	--	--	--	--	--	--	--
12-lead ECG	X	--	--	--	--	--	--	--	--	--	--
Cardiac telemetry per institutional protocol[b]	X	←	—	—	—	—	—	—	—	—	→
Physical Exam	X	--	--	--	--	--	--	--	--	--	X
Vital signs[c]	X		X	X	X	X	X	X	X	X	X
Concomitant medications	X	←	—	—	—	—	—	—	—	—	→
Adverse events collection	X	←	—	—	—	—	—	—	—	—	→
Place right heart catheter	X	--	--	--	--	--	--	--	--	--	--
PD assessments: PVR, MVO_2, Hgb, RVP, PAP CO, PVR, RAP, oxygen consumption, PCWP (Baseline only)[d], heart rate, SpO_2, systemic blood pressure[e]	X	--	X	X	X	X	X	--	X	X	--

Treatment Period (Study Day 1 to Study Day 2)											
	Pre-TPIP Administration	**TPIP Administration**	**Post-TPIP Administration**								
Procedure	Day 1 Baseline	Time 0	30 min	60 min	90 min	2 h	3 h	4 h	8 h	24 h	24 h to discharge
Administer TPIP	--	X	--	--	--	--	--	--	--	--	--
Remove RHC	--	--	--	--	--	--	--	--	--	--	X
Discharge/Safety Follow-up Instructions	--	--	--	--	--	--	--	--	--	--	X

[a] See Section 10.2, Table 7 for specific laboratory tests.
[b] Routine cardiac telemetry readings will not be collected as study data unless they pertain to a relevant adverse event.
[c] Heart rate, systemic blood pressure, and SpO_2 are required PD measurements and will be collected as scheduled. They may be measured with pulse oximetry for heart rate and SpO_2 and an automated inflatable arm cuff for blood pressure. Temperature and respiratory rate may be measured per institutional inpatient protocol. Respiratory rate will be measured as part of pulmonary gas exchange testing, if performed.
[d] PCWP is measured at Baseline only to ensure study eligibility (Section 5.1).
[e] Systemic blood pressure must include 3 values: systolic, diastolic, and mean arterial pressure.
CO = cardiac output; Hgb = hemoglobin; MVO_2 = mixed venous oxygen saturation; PAP = pulmonary arterial pressure; PVR=pulmonary vascular resistance; RAP = right atrial pressure; RVP = right ventricular pressure; SpO_2 = arterial blood oxygen saturation; WOCBP = woman of childbearing potential

Table 3: PK and PD Biomarker Sampling Schedule, Single-Dose Period, INS1009-201

--	**Baseline Pre-TPIP Administration**	**TPIP administration**	**Post-TPIP Administration**						
Time	--	0	30 (± 10) mins	60 (± 10) mins	2 h (± 20) mins	4 (± 1) h	8 (± 2) h	24 (± 2) h	48 (± 4) h
PK sampling[a]	X	--	X	X	X	X	X	X	X
Biomarker sampling[b]	X	--	--	--	--	X	X	--	--

[a] PK sampling for treprostinil palmitil and treprostinil; each PK sample will be approximately 10 mL.
[b] Each biomarker sample will be approximately 5 to 7 mL.

Table 4: Schedule for Optional Procedures and Assessments, Inpatient Treatment Period, INS1009-201

Inpatient Treatment Period (Study Day 1 to Study Day 2)										
	Pre-TPIP Administration	**TPIP Administration**	**Post-TPIP Administration**							
Procedure	Study Day 1 Baseline	Time 0	2-8 hr	4-8 hr						
Transthoracic echocardiogram (LVEF,TVR maximum velocity, TAPSE, end diastolic right ventricular volume)	X	--	X	--						
Pulmonary CT scan (total blood volume, blood volume in vessels < 5 mm^2)	X	--	--	X						
--	**Pre-TPIP Administration**	**TPIP Administration**	--							
--	Study Day 1 Baseline	Time 0	30 mins	60 mins	90 mins	2 h	3 h	4 h	8 h	24 h
Resting respiratory gas exchange assessment[a] (respiratory rate, minute ventilation, VCO_2, ETO_2, $ETCO_2$, SpO_2	X	--	X	X	X	X	X	--	X	X

[a] Resting respiratory gas assessment parameters are collected at the same time points as RHC parameters.

NOTE: Parameters to be measured for each procedure are in parentheses.

CT=computerized tomography; $ETCO_2$ =end tidal carbon dioxide concentration; ETO_2,=end tidal oxygen concentration; LVEF=left ventricular ejection fraction; SpO_2=arterial blood oxygen saturation; TAPSE=tricuspid annular plane systolic excursion; TVR=tricuspid valve regurgitation; VCO_2,=carbon dioxide production

Table 5: Schedule of Activities for Screening and Follow-up, Extended Use Treatment Period, INS1009-201

Procedure	Screening[a]	Follow-up
	EUT Study Day 1 (± 3 days)	EUT Study Day 142 (± 3 days)
Informed Consent	X	--
Inclusion/Exclusion Criteria	X	--
Demographics	X	--
Smoking Status	X	--
Height, Weight, BMI Calculation	X	--
Prior/Concomitant Medications	X	X
Urine Pregnancy Test (WOCBP only)	X	X
Hematology, Clinical Chemistry (Table 7)	X	--
NT-pro-BNP Sample (if needed, Section 5.1)	X	--
Vital Signs	X	--
6 Minute Walking Distance Test (if needed, Section 5.1)	X	--
Adverse Events[b]	X	X

[a] Participants will only be screened at EUT Day 1 if they enter the EUT period beyond 30 days after beginning the single-dose period (e.g., beyond the initial 30 day follow-up period).
[b] AEs for the period from the Study Day 30 follow-up until the enrollment in the EUT period will be collected during participants' screening for the EUT.
BMI = Body Mass Index; EUT = extended use treatment; WOCBP = woman of childbearing potential

Table 6: Schedule of Activities for the Optional Extended Use Treatment Period, INS1009-201

Period	**Extended Use Treatment Period**						**Follow-Up**	**E/D[a]**
Week	**EUT W1**	**EUT W2**	**EUT W3**	**EUT W5**	**EUT W10**	**EUT W16**	**EUT W20[b]**	
Day	**EUT D1 (Screening[c] and Baseline)**	**EUT D10 (± 3 days)**	**EUT D21 (± 3 days)**	**EUT D35[d] (± 3 days)**	**EUT D70 (± 3 days)**	**EUT D112 (± 3 days)**	**EUT D142 (± 3 days)**	
Visit	**EUT V1**	**EUT V2**	**EUT V3**	**EUT V4**	**EUT V5**	**EUT V6**	**EUT V7**	
Inclusion/exclusion	X[c]							
Prior/concomitant medications	→	→	→	→	→	→	→	
Pregnancy test (WOCBP only)[e]	X[c]	→	→	→	→	→		X
Vital signs[f]	X[c]	X	X	X	X	X		X
6MWD test	X					X		
Hematology, clinical chemistry [g]	X[c]							
12-lead ECG	X[c]							
NT-pro-BNP Sample	X					X[c]		
Optional pulmonary CT scan (total blood volume, blood volume in vessels < 5 mm^2)	X					X		
Study drug distribution[h]	X	X	X	X	X	X		
Study drug self-administration re-assessment[i]		X	X	X	X	X		
Targeted physical examination[j]	X		X	X	X			
Study drug accountability[k]		X	X	X	X	X	X[l]	

Period	Extended Use Treatment Period						Follow-Up	E/D[a]
Week	EUT W1	EUT W2	EUT W3	EUT W5	EUT W10	EUT W16	EUT W20[b]	
Day	EUT D1 (Screening[c] and Baseline)	EUT D10 (± 3 days)	EUT D21 (± 3 days)	EUT D35[d] (± 3 days)	EUT D70 (± 3 days)	EUT D112 (± 3 days)	EUT D142 (± 3 days)	
Visit	EUT V1	EUT V2	EUT V3	EUT V4	EUT V5	EUT V6	EUT V7	
Dosing diary	→							
Adverse events[m]	→							

[a] Participants who enroll in the optional EUT period and discontinue before the end of study will be classified as early discontinuations.
[b] Follow-up telephone call or visit will be 30 days after the EUT Week 16 visit.
[c] Participants will undergo assessments for screening at EUT Day 1 if they enter the EUT period beyond 30 days after beginning the single dose period (e.g., beyond the initial 30 day follow-up period).
[d] At the Investigator's discretion, an increase of 1 dose level may be allowed at EUT Week 5 if the participant has not achieved the 640 µg dose.
[e] Pregnancy test: Urine pregnancy tests will be performed in-clinic at EUT Baseline (EUT Day 1) in WOCBP. WOCBP will be provided home pregnancy test kits with instructions to conduct the pregnancy tests every 30 days or more if required during the treatment and follow-up periods. Study site personnel will contact the participant every 30 days by telephone and record the pregnancy test results. An additional on-site urine test must be performed prior to starting any procedure that requires the use of ionizing radiation.
[f] Vital signs: Includes body temperature (°C), pulse rate (bpm), respiratory rate (breaths/min), blood pressure (systolic, diastolic and mean arterial [mmHg]), and SpO_2. Vital signs will be measured at EUT Screening/Baseline (EUT Day 1), EUT Week 2, EUT Week 3, EUT Week 5, EUT Week 10, and EUT Week 16 and at the Early Discontinuation visit, if appropriate.
[g] See Table 7 for additional information.
[h] Participants will receive study drug supply on EUT Day 1 and at EUT Week 2, EUT Week 3, EUT Week 5, and EUT Week 10 visits. Participants who undergo a study drug taper will receive study drug supply at the EUT Week 16 visit. A telephone call from study personnel or the Investigator will be placed to participants assigned to a study drug taper to check on the participant's well-being; timing of the telephone call will be based on the Investigator's discretion, and any adverse events will be captured on the CRF.
[i] Assessment of study drug self-administration: Study drug self-administration will be overseen by study site personnel at all in-clinic visits.
[j] The targeted physical examination will be performed at Week 3, Week 5, and Week 10 prior to study drug administration. The targeted physical exam includes cardiovascular (cardiac auscultation, assessment of peripheral pulses and edema) and pulmonary assessments (pulmonary auscultation).
[k] Participants will return unused capsules and used capsules and devices to the study site at the Week 2, Week 3, Week 5, Week 10, and Week 16 visits.
[l] Participants who undergo a study drug taper will return unused capsules and used capsules and devices to the study site at a follow-up visit.
[m] AE collection from the 30 day follow-up period in the single-dose period to enrollment in the EUT period will be queried during EUT screening; All other AEs and SAEs will be collected from EUT Day 1 and followed up as described in Section 8.3.3.
6MWD = 6-minute walk distance; CT = computerized tomography; CRF = case report form; D = day; E/D = early discontinuation; EUT = extended use treatment; NT-pro-BNP = N-terminal pro B-type natriuretic peptide; W = week; WOCBP = woman of childbearing potential; V = Visit

2. INTRODUCTION

Pulmonary hypertension (PH), a hemodynamic state characterized by resting mean PAP > 20 mmHg per updated guidelines (Simonneau et al., 2019), is generally classified into 5 groups based on the underlying pathology: Group 1 is PH due to pulmonary vascular disease, also known as pulmonary arterial hypertension (PAH); Group 2 is PH due to left heart disease; Group 3 is PH due to lung disease or hypoxia; Group 4 is PH due to chronic thromboembolic disease or other pulmonary vasculature obstruction; Group 5 is miscellaneous PH syndromes caused by a variety of disorders such as hemolytic anemias and sarcoidosis (Thenappan et al., 2018).

In Group 1 PH (PAH), the resting mean PAP > 20 mmHg occurs in the setting of normal pulmonary arterial wedge pressure of ≤15 mm Hg with PVR of ≥3 Wood Units (WU) (McLaughlin et al., 2009). In PAH the pulmonary vasculature is affected by vasoconstriction, vascular remodeling, increased rigidity of vessel walls and vascular fibrosis. These vascular anomalies increase PVR, which leads to increases in right ventricular afterload, and a cascade of maladaptive changes to the heart including right ventricular hypertrophy, ischemia and fibrosis, reducing right ventricular function and eventually leading to right ventricular failure and death (Thenappan et al., 2018). The pulmonary vascular lesions of PAH may be idiopathic, hereditary, or occur as a complication of drug use (e.g., anorexigens), connective tissue disease, portal hypertension, congenital cardiac malformations or HIV infection (Hoeper et al., 2017).

Data from PAH registries around the world (Thenappan et al., 2018) estimate a global incidence ranging from 2.0 to 7.6 cases per million adults per year, with a prevalence of 11 to 26 cases per million adults; the incidence in females is approximately 4 times that in males. Most registries report a mean age of onset ranging from approximately 36 to 53 years. While overall median survival has improved from 2.8 years in the 1980's to 6 years currently, mortality is high, with 1 year survival ranging from 68% to 93% and 5 year survival ranging from 21% to 65%. Nearly half of the patients in these registries have PAH of idiopathic, heritable or anorexigen-induced origin.

PAH is a debilitating progressive disease that causes a wide range of non-specific symptoms including, dyspnea, shortness of breath, chest pain, fatigue, generalized weakness and exertional syncope (Delcroix and Howard, 2015), severely affecting the patient's physical mobility, emotional and social well-being, ability to perform activities of daily living and overall quality of life. Pharmacological treatments are available to mitigate disease symptoms and slow disease progression, but treatment-related AEs, inconvenience and side effects can be treatment-limiting and negatively influence the patient's daily life (Delcroix and Howard, 2015).

The currently available pharmacologic treatments for PAH include calcium channel blockers, guanylate cyclase stimulators, endothelin receptor antagonists, phosphoesterase type 5 inhibitors, and prostanoids and prostacyclin agonists. Prostanoids, such as TRE, are among the most effective medications for the treatment of PAH. However, they are limited by the need for inconvenient and frequent drug administration and dose-limiting side effects (Thenappan et al., 2018).

2.1. Study Rationale

Treprostinil palmitil (TP) is an inactive prodrug of treprostinil (TRE). TPIP is a dry powder for inhalation formulation of TP. TPIP is being developed for the treatment of PAH. TPIP is expected to provide extended release of TRE in the lung with the goals of less frequent and more convenient and consistent dosing while reducing the frequency and severity of dose-limiting side effects associated with the currently approved forms of TRE. TP has been previously studied in healthy volunteers as an inhalation suspension (treprostinil palmitil inhalation suspension, TPIS), in single doses up to 340 µg (Study INS1009-101), and TPIP has been previously studied in a single ascending dose/multiple ascending dose (SAD/MAD) study in healthy volunteers (Study INS1009-102).

No studies of TP or TPIP have been conducted in participants with PAH. Study INS1009-201 is an open label, non-randomized, single- dose study designed to evaluate the safety, pharmacokinetics (PK), and pharmacodynamic (PD) effects of a single dose of TPIP in participants with PAH. An optional EUT period was added to maximize participant convenience and accessibility.

2.2. Background

Treprostinil is a tricyclic benzidene analogue of prostacyclin. As such, TRE has vasodilatory and anti-platelet activity within the pulmonary vascular system, thereby reducing blood flow resistance and improving the clinical state, functional class, exercise capacity, and quality of life of patients with PAH (Vachiery and Naeije, 2004).

Treprostinil has a high potency but is short-lived in the body and must be administered by continuous IV or SC infusion, or given multiple times per day by inhaled or oral routes. At present, TRE is available in the United States in formulations of IV or SC infusion (Remodulin Package Insert, 2018), oral extended-release tablets (Orenitram Package Insert, 2019), and inhalation solution (Tyvaso Package Insert, 2017) to treat PAH. The clinical experience with TRE suggests that most of the AEs experienced are related to its effects on prostanoid metabolism (e.g., headache, nausea, diarrhea, flushing, bleeding, and hypotension). Dose-limiting side effects correlate to systemic plasma concentrations of TRE.

Treprostinil palmitil is a hexadecyl ester prodrug of TRE. In the lung, TP is hydrolyzed by esterase to TRE and hexadecanol. TPIP is a dry powder formulation of TP designed to provide sustained release of TRE in the lung over a prolonged period, thus providing prolonged vasodilation in the lung vasculature. This effect was demonstrated in a rat acute hypoxia model that showed a maximal reduction in PAP through the 3-hour monitoring limit with TP, while the effect of inhaled TRE started to diminish by 1 hour and was completely gone after approximately 2.5 hours. The prolonged lung exposure and pharmacological action of TRE achieved with sustained release from the prodrug TP aims to reduce both dosing frequency and side effects driven by fluctuations of plasma levels of TRE.

Treprostinil palmitil was well tolerated in rats and dogs following 16-week once-daily inhalation. At no observed adverse effect level (NOAEL) doses, the plasma C_{max} and AUC of TRE at steady

state in rats (2000 µg/kg/day) were 11 ng/mL and 73 ng*h/mL, respectively, and in dogs (250 µg/kg/day) were 1.2 ng/mL and 13 ng*h/mL, respectively.

Thus far, TP has been studied in 2 Phase 1 studies of healthy participants: An SAD study of TPIS (Study INS1009-101) and an SAD/MAD study of TPIP (Study INS1009-102). Single doses of up to 675 µg and multiple doses of up to 225 µg for 7 days were administered to healthy participants. Overall, TP was well tolerated, with largely mild treatment-emergent adverse events (TEAEs) and an adverse effect profile consistent with that of inhaled prostacyclin analogs. Treprostinil exposures increased approximately dose-proportionately, were similar between TPIS and TPIP, and showed no accumulation with QD dosing. Doses of TP achieved were several-fold higher than label-indicated target dose of inhaled treprostinil (54 µg). When comparing TPIS to inhaled treprostinil, TP had a 10-fold lower maximum plasma concentration (89.0 pg/mL vs. 958 pg/mL) and a markedly longer half-life (5.69 hours vs. 0.485 hours) than inhaled treprostinil at the molar equivalent dose. Half-life of TP was even longer with TPIP, ranging from 8.67 to 11.6 hours. These differential PK of TP may offer therapeutic advantages over treprostinil with the need for less frequent administration (QD vs QID), fewer adverse effects, and potentially improved efficacy with higher tolerated dose.

Additional information regarding the results of non-clinical and clinical studies of TP are provided in the Investigator's Brochure.

2.3. Benefit/Risk Assessment

Detailed information about the known and expected benefits and risks and reasonably expected TEAEs for TPIP from clinical and non-clinical studies may be found in the Investigator's Brochure.

2.3.1. Risk Assessment

There is no TPIP experience in participants with PAH; however, the active component, TRE, like other prostanoids and their agonists, has a well-characterized safety profile. This will help enable participants to be adequately monitored during the study.

Insmed has conducted a SAD study of TPIS in healthy volunteer participants, with safety and tolerability findings similar to those of other prostanoids (Study INS1009-101). In this study, 32 TEAEs were reported for 11 of 18 participant who received TPIS. No fatal TEAEs were reported and no TEAEs led to the withdrawal of participants. One participant who received a single dose of TPIS containing 340 µg of TP experienced several interrelated AEs that culminated in 2 TEAEs of severe and life-threatening intensity, as judged by the Investigator. The Investigator believed a severe TEAE of micturition syncope was precipitated by a TEAE of chest pain, which was assessed as probably related to the study IMP and increased vagal tone during micturition. Follow-up evaluation by an external cardiologist reveled that the participant had Tachy-Brady syndrome. A serious adverse event (SAE) of cardiac pause/nodal arrhythmia was reported for this participant and assessed as probably related to TPIS. Beyond this event, 7 TEAEs were assessed as being of moderate intensity and 23 TEAEs to be of mild intensity.

The most frequently reported TEAEs among participants receiving TPIS were cough (5 events for 5 participants), dyspnea (4 events for 4 participants), and throat irritation (4 events for

4 participants). Other TEAEs reported for more than 1 participant receiving TPIS included nausea (3 events for 3 participants) and headache (2 events for 2 participants).

There was a dose-related trend in the incidence of TEAE reporting with increasing dose levels of TPIS: 5 TEAEs were reported for 2 participants after receiving a single TPIS dose containing 85 µg of TP, 7 TEAEs were reported for 4 participants after receiving a single TPIS dose containing 170 µg of TP, and 20 TEAEs were reported for 5 participants after receiving a single TPIS dose containing 340 µg of TP.

Safety results from a recently conducted SAD/MAD study of TPIP in healthy volunteer participants (Study INS1009-102) support the TPIP dosing and management of participant safety for this study. In this study, TPIP was generally safe and well tolerated. TEAEs reported with TPIP were consistent to those seen with other inhaled prostanoid therapies. The majority of TEAEs were judged by the Investigator to be of mild intensity; there were few moderate TEAEs and no severe TEAEs across the study. No participants reported AEs of severe intensity, and no SAEs were reported. There was 1 participant in the MAD panel who discontinued after 2 doses. TEAEs were more frequent with increasing TPIP doses. In the MAD panel, participants titrated from TPIP 112.5 µg QD to 225 µg QD experienced fewer TEAEs than those who received 225 µg QD at treatment initiation, and all TEAEs were of mild severity.

Nonserious adverse events (AEs) observed in clinical studies to date are known for the pharmacological class of prostacyclin vasodilators and are considered expected for TPIP. No serious adverse reactions are considered expected for TPIP. Please refer to the Reference Safety Information in Section 6.1 of the Investigator's Brochure.

Risks inherent in study procedures and in the inpatient treatment period will be managed per Investigator and institutional processes. It is possible that the RHC-dependent Baseline parameters may indicate that the participant does not meet study inclusion criteria, may meet exclusion criteria, or is otherwise not suitable for study participation; in this case the Investigator may end the RHC procedure and not administer TPIP.

In general, an RHC is left in place for 30 to 60 minutes to take necessary measurements. This study requires the RHC to be in place for approximately 24 hours. Excess risks with prolonged placement of the RHC may include but not be limited to dislodging of the RHC, infection, bleeding, clot formation, and participant discomfort.

2.3.2. Benefit Assessment

TPIP is being developed for the treatment of PAH. TPIP may or may not result in beneficial effects for participants with PAH by providing extended release of TRE in the lung with less frequent and more convenient dosing.

2.3.3. Overall Benefit: Risk Conclusion

Although participants may or may not benefit individually from this study, risks to their well-being will be carefully monitored and managed throughout their participation. Insmed considers the risks to be appropriate to the value of the knowledge gained in this study about the characteristics of this promising therapy. The well-characterized safety profile of TRE and the

continued safety monitoring by both the Investigator and SRC (in the inpatient treatment period, observation period, and optional EUT period, if applicable) will minimize risk to participants. Most TEAEs observed with exposure to this drug are events known to be associated with prostanoids and their agonists. Study inclusion and exclusion criteria will help to ensure that only appropriate participants are enrolled. Risks involved with study procedures and settings will be managed by the relevant Investigator and institutional processes.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	**Primary**
• To evaluate the safety and tolerability of single doses of TPIP in participants with PAH	• Frequency of TEAEs
Secondary	**Secondary**
• To evaluate the effects of single doses of TPIP on PVR in participants with PAH over the first 24 hours following administration	• Change from Baseline in PVR at 8 and 24 hours after TPIP administration
• To evaluate the PK of TRE in participants with PAH	• C_{max}, t_{max}, $AUC_{t1–t2}$, $AUC_{0–\infty}$, $t_{1/2}$ of TRE in plasma
Exploratory	**Exploratory**
• To evaluate the PD effects of single doses of TPIP in participants with PAH over 24 hours following administration	• Change from Baseline in PVR, PAP, RVP, RAP, CO, oxygen consumption, MVO_2, SpO_2, heart rate, systemic blood pressure, hemoglobin, at selected time points after TPIP administration
• To evaluate the effect of single doses of TPIP on selected biomarkers in participants with PAH over 24 hours following administration	• Change from Baseline in selected biomarker concentrations at selected time points after TPIP administration
• To evaluate changes in clinical laboratory parameters in participants with PAH after TPIP administration	• Clinically relevant change from Baseline in hematology, coagulation and clinical chemistry parameters (Section 10.2, Table 7)
• To evaluate the PK of TP in participants with PAH	• Plasma PK parameters of TP, such as C_{max}, t_{max}, $AUC_{t1–t2}$, $AUC_{0–\infty}$, $t_{1/2}$, CL/F and Vd/F

• To evaluate the PK of TRE in participants with PAH	• Plasma PK parameters of TRE, such as C_{max}, t_{max}, $AUC_{t1–t2}$, $AUC_{0–\infty}$, $t_{1/2}$, CL/F and Vd/F
• To evaluate the effects of TPIP on resting respiratory gas exchange in participants with PAH[a]	• Change from Baseline in respiratory rate, minute ventilation, VCO_2, ETO_2, $ETCO_2$, SpO_2 over 24 hours after TPIP administration
• To evaluate the effects of TPIP on parameters of right ventricular function in participants with PAH as measured by transthoracic echocardiogram[b]	• Change from Baseline in LVEF, TVR maximum velocity, TAPSE, and end diastolic right ventricular volume at 2 to 8 hours after TPIP administration
• To evaluate the effects of TPIP on pulmonary vasculature and blood flow parameters in participants with PAH as measured by pulmonary CT scan[c]	• Change from Baseline in total blood volume, blood volume in vessels < $5mm^2$ at 4 to 8 hours after TPIP administration

[a] Respiratory gas exchange testing optional at Investigator discretion
[b] Echocardiogram optional at Investigator discretion
[c] Pulmonary CT scan optional at Investigator discretion
$AUC_{0–\infty}$ = area under the concentration time curve from time zero to infinity; AUC_{t1-t2} = area under the concentration time curve from time zero to last sampling time point with measurable concentration; C_{max} = maximum observed concentration after drug administration; CL/F = apparent total clearance; CO = cardiac output; CT = computerized tomography; $ETCO_2$ = end tidal carbon dioxide concentration; ETO_2 = end tidal oxygen concentration; LVEF = left ventricular ejection fraction; MVO_2 = mixed venous oxygen saturation; PAH = pulmonary arterial hypertension; PAP = pulmonary arterial pressure; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PVR = pulmonary vascular resistance; SpO_2 = arterial blood oxygen saturation; TAPSE = tricuspid annular plane systolic excursion; TEAE = treatment emergent adverse event; TP = treprostinil palmitil; TPIP = treprostinil palmitil inhalation powder; TRE = treprostinil; TVR = tricuspid valve regurgitation; t_{max} = time of maximum observed concentration following drug administration; $t_{1/2}$ = elimination half-life; Vd/F = apparent volume of distribution at terminal phase; VCO_2 = carbon dioxide production

3.1. Exploratory Objectives and Endpoints for the Optional Extended Use Treatment Period

Objectives	Endpoints
Exploratory	Exploratory
• To evaluate the safety and tolerability of TPIP in participants with PAH	• Frequency of TEAEs during EUT

• To assess the effect of TPIP on exercise capacity	• Change from Baseline in 6MWD distance at EUT Baseline to EUT Week 16

6MWD = 6-minute walk distance; EUT = extended use treatment period; PAH = pulmonary arterial hypertension; TEAE = treatment emergent adverse event; TPIP = treprostinil palmitil inhalation powder

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2a, open label, non-randomized study to assess the safety, tolerability, PD effects and PK of TPIP administered to participants with WHO Group 1 PH (PAH). This is the first patient study of TPIP. Each participant will receive a single dose of TPIP. The first participant should receive a dose containing 112.5 µg; if the 112.5 µg formulation is not available due to expiration date, the first participant may receive the 80 µg formulation. The TP dose level for each subsequent participant will be determined following review and adjudication of all available safety, PK, and PD data from the previous participant(s) by the SRC (Section 10.1.7). There is an optional extended-use period for 16 weeks in participants who have completed the core, single-dose period.

This is a "proof of mechanism" study designed to investigate the following:

1. The safety and tolerability of TPIP in participants with PAH,
2. The relationship between the PK and PD effects of TPIP in participants with PAH, and
3. The duration of the PD effects of a single dose of TPIP in participants with PAH.

The cardiopulmonary and overall functional status of participants with PAH can be labile and medical instability can develop quickly. The study is designed to provide maximal safety and minimal risk to participants. As such, there considerable flexibility built into the protocol to allow Investigator discretion with the frequency, timing, and/or conduct of PD and PK assessments to ensure participant safety. Because the study requires an overnight inpatient treatment period, institutional requirements for elective inpatient admissions, which may vary from site to site, will be followed.

For individual participants, the study will consist of an outpatient screening period lasting up to 30 days. The inpatient treatment period will start on Study Day 1 and is expected to last overnight into Study Day 2. Outpatient PK sampling and safety follow-up at 48 (± 4) hours post TPIP dose will extend into Study Day 3. A remote safety follow-up visit is scheduled for Study Day 30 (± 2 days). The 48 hour PK visit will also include safety assessments including ECG, clinical laboratory evaluations, vital signs, physical examination, and AE collection (Table 1). The safety follow-up period will conclude with a remote (telephone or telemedicine) visit on Study Day 30 (± 2 days). The screening, treatment, and follow-up periods for the core, single-dose portion of the study are expected to be 62 days or less. An EUT period of 16 weeks will be optional for participants that complete the single-dose period, followed by a 30 day follow-up (± 3 days). This extends study participation to 142 days after enrollment in the EUT period.

4.1.1. Screening Period

The initial screening period will be up to 30 days. Required screening assessments are shown in Table 1. Participants who fail one or more screening assessments may be re-screened twice at the Investigator's discretion in order to meet study entry criteria. See Section 5.4 for additional information regarding participants who fail screening and/or are re-screened.

Participants who enter the optional EUT period more than 30 days after beginning the single-dose period (e.g., beyond the initial 30 day follow-up period) will be screened to ensure they continue to satisfy inclusion and exclusion criteria. Extended use treatment period screening assessments are shown in Table 5.

4.1.2. Inpatient Treatment Period

4.1.2.1. Baseline Procedures and Assessments

The inpatient treatment period will be on Study Days 1 and 2. The participant may be required to undergo pre-admission assessments required by the Institution for elective admission, for example testing for common infectious pathogens. Signature of institutional elective admission documents and consents to procedures may be required. Data from required institutional assessments and consents will not be routinely collected as part of study data unless they pertain to a relevant AE or study endpoint.

Participants will be admitted to an inpatient care setting such as an ICU, cardiac catheterization laboratory or other similar setting. They will have Baseline laboratory and safety assessments as shown in Table 2. An RHC will be placed for Baseline assessment of cardiopulmonary hemodynamics prior to TPIP administration and intermittent assessments of cardiopulmonary hemodynamics for 24 hours following TPIP administration. Institutional procedures and protocols for placement, care, monitoring, and removal of the RHC will be carried out but will not be collected as study data unless relevant.

Some procedures and assessments for exploratory endpoints may not be offered at all sites. Participants will be asked to give informed consent only to those procedures that are being conducted by their Investigator at their site. These procedures include the following:

- Transthoracic echocardiogram at Baseline and during a 2 to 8 hour window after TPIP administration (Table 4).
- Pulmonary computerized tomography (CT) scan at Baseline and during a 4 to 8 hour window after TPIP administration (Table 4).
- Resting respiratory gas exchange assessment at Baseline and intermittently after TPIP administration for up to 24 hours (Table 4). Resting respiratory gas exchange assessments will be standardized, with all participating investigators using similar equipment and procedures.

For example, an Investigator who is doing only RHC and resting respiratory gas exchange assessments for this study will obtain informed consent for those procedures only and will not offer or ask the participant for informed consent for transthoracic echocardiogram or pulmonary CT scan as part of this study.

Following completion of all Baseline assessments, including Baseline blood draws for PK and PD biomarkers (Table 3), the prescribed single dose of TPIP will be administered (Table 2).

4.1.2.2. Post-TPIP Administration

Following TPIP administration, participants will have intermittent safety, clinical laboratory, PK, and PD assessments, as specified in the SoA (Table 2, Table 3, and Table 4). The study is designed to allow maximum flexibility for interventions and assessments at the discretion of the Investigator and institutional policies and procedures to ensure participant safety. At any time, the Investigator has the option to discontinue assessments for participant safety or tolerability reasons. Additional laboratory and/or hemodynamic assessments may be performed as deemed necessary for participant safety. Following completion of scheduled events, the Investigator has the option of continued laboratory and/or hemodynamic monitoring as deemed appropriate for participant safety.

If, in the interest of participant safety, the Investigator omits scheduled assessments/procedures or performs additional assessments/procedures, the reason for doing so must be reported on the CRF as an AE in order to avoid a protocol violation.

Following completion of protocol-required assessments and removal of the RHC, the participant will be discharged from the inpatient setting when deemed safe by the Investigator. Investigator and institutional usual care protocols for participant discharge and follow-up for an RHC procedure will apply.

4.1.2.3. Post-discharge Outpatient Visits for PK Sampling and Safety Follow-up

The participant will be required to return as an outpatient for the 48 (± 4) hour post-TPIP administration PK sample. Additional safety assessments such as ECG, physical examination, vital signs, AE collection, and clinical laboratory evaluations will be completed at the 48 hour visit. Female participants who are women of child-bearing potential (WOCBP) will be given a self-administered pregnancy test kit with instructions to self-administer the test and report the results on the day of the Study Day 30 safety follow-up visit (Section 4.1.3).

4.1.3. Safety Follow-up

A remote (telephone call or telemedicine) safety follow-up visit is scheduled for Study Day 30, at which time participants who are WOCBP will also be asked to report the results of the self-administered pregnancy test they were given at the 48 hour post-TPIP follow-up visit (Section 4.1.2.3, Table 1).

4.1.4. Optional Extended Use Treatment Period

All participants will be allowed to enter the optional 16 week EUT period after the completion of the inpatient treatment period and final PK sample collection. Entry into the optional EUT period will be at participant and Investigator discretion. A gap between the inpatient treatment period and EUT period is expected, but not required, and can be up to 6 months.

After collection of the final PK sample, all participants will be allowed optional continued access to IMP for 16 weeks (includes a 3-week titration period) from first administration in the EUT period. At the Investigator's discretion, participants may undergo a study drug taper for up to 2 weeks after the Week 16 visit to help facilitate a safe withdrawal from study drug.

Participants will be screened to ensure they meet inclusion and exclusion criteria if they enter the EUT period more than 30 days after beginning the single-dose period (e.g., beyond the initial 30 day follow-up period) (Table 5).

Participant in-clinic study visits will be scheduled for EUT Baseline (EUT Day 1), EUT Week 2, EUT Week 3, EUT Week 5, EUT Week 10, and EUT Week 16.

The CT scan will be performed according to instructions provided by the CT scan vendor.

There will be a second safety follow-up visit 30 days (± 3 days) after EUT Week 16 for participants who elect to enter the EUT period.

4.1.5. Open-label Extension Study

When available, participants may be eligible to enroll in a separate OLE study that will have a duration of approximately 2 years. Details of the planned OLE study will be provided in a separate protocol.

4.2. Scientific Rationale for Study Design

The study is designed to understand the safety and acute PK and PD effects of TPIP in participants with PAH, the intended patient population. Intensive monitoring via RHC in an appropriate inpatient setting is essential to understand how TPIP affects cardiopulmonary hemodynamics and to elucidate relationships between dose, PK, and PD effects. Some assessments and study activities for exploratory endpoints are considered optional depending on Investigator preference and/or based on study site capabilities and procedures (Table 4).

4.3. Justification for Dose

4.3.1. Inpatient Treatment Period (Single-dose)

Treprostinil palmitil has been previously studied in healthy volunteer participants as a liquid suspension for inhalation (TPIS) and has now been formulated as a dry powder for oral inhalation (TPIP). Data from pre-clinical pharmacology and safety studies supported the initiation of human studies with TPIS. Preclinical studies in rats and dogs showed that the plasma kinetics of TRE and TP after dosing with TPIP are similar to those of TPIS. Additional clinical PK and safety data from healthy participants after SAD and MAD dosing with TPIP supported the chosen study design and dose. For further information on the non-clinical pharmacology and safety studies of TPIS and TPIP, please refer to the Investigator's Brochure.

The current study utilizes the clinical experience of TPIS from Study INS1009-101 in healthy volunteer participants and the INS1009-102 SAD/MAD study of TPIP in healthy volunteer participants. In Study INS1009-101, doses of TPIS were administered in multiples of 85 µg TP to include 170 µg (2 × 85 µg) and 340 µg (4 × 85 µg) of TP. The systemic exposure for TRE at 340 µg TP was low (AUC < 2.5 ng*h/mL) with an elimination $t_{1/2}$ of approximately 7 hours.

Data from the INS1009-102 SAD/MAD study of TPIP reinforced the study design and informed maximum dosage for the optional extended use portion of the study (Section 4.3.2). In the first SAD portion of INS1009-102 (SAD1), 18 participants were randomized to 1 of 3 TP dose levels

of TPIP: 112.5 µg, 225 µg, or 450 µg of TP (6 participants at each dose). Treprostinil peak concentrations in the SAD portion were attained at 1.5 to 3 hours post-dose; C_{max} and AUC were dose-dependent and approximately proportional to the increase of dose; and elimination $t_{1/2}$ was 8.7 to 11.6 hours. Total treprostinil exposure (AUC) of treprostinil was found to be dose proportional following a single administration of TPIP across the dose range of 112.5 µg to 675 µg.

Based on this Phase 1 study experience, the first participant is expected to be dosed with 112.5 µg of TP. However, if the 112.5 µg formulation is not available due to expiry, it is acceptable to use the 80 µg formulation (described in more detail in Section 4.3.2). Administration of TPIP will be via inhalational dry powder packaged in single actuation capsules. Each capsule with 112.5 µg of TP contains the molar equivalent of 71 µg of TRE and 7.5 mg of dry powder. Approximately 85 µg of TP (54 µg of TRE equivalent) will be emitted from the dry powder inhalation device for this formulation. This is comparable to a single administration of Tyvaso for patients with PAH with the target dose being 54 µg QID. Single doses of up to 90 µg of Tyvaso have been administered in clinical studies of healthy volunteer participants (Tyvaso Package Insert, 2017).

Each participant will receive a single dose administration of TPIP. A TPIP dose containing 112.5 µg of TP (or 80 µg, depending on 112.5 µg expiry) will be given to the first participant in Study INS1009-201. All available data (PD, PK, safety) from the first participant will be assessed and evaluated by the SRC. Following this evaluation, the SRC will determine if it is safe to continue the study, the TPIP dose level and any changes to safety PD and PK assessments for the second participant (Figure 3). This process will be repeated using the total accrued data of all completed participants prior to determining the TPIP dose for each subsequent participant. There will be no simultaneous dosing of inpatient participants; each participant will be treated as an individual case for evaluation. The TP dose level for each subsequent participant may be increased, held stable or lowered, depending on the accumulating data from previous participants up to a maximum of 675 µg. TPIP dosing may also be stopped at any dose level as determined by the SRC.

4.3.2. Optional Extended Use Treatment Period

Selection of once-daily inhalation of TPIP at 80 – 640 µg was based on clinical PK and safety data from healthy participants, predicted efficacious dose levels using pre-clinical data, safety margin from rat and dog NOAEL doses, and Tyvaso® clinical experience.

In Phase 1 studies, TRE PK was linear, and the systemic exposure was dose proportional. Single doses of up to 675 µg and multiple doses of up to 225 µg TPIP QD for 7 days were generally well tolerated. Most AEs observed were mild in severity and consistent with the safety profile of other prostanoid therapies.

Based on exposures following a single dose of TPIP 675 µg in Study INS1009-102, TRE exposures in this study are not anticipated to exceed those following administration of the currently approved treprostinil product, Remodulin®. Treprostinil exposures following a continuous IV infusion of 10 ng/kg/min Remodulin (C_{max} 1,470 pg/mL; AUC 25,690 pg*h/mL) are reported to be 2.1-fold and 4.7-fold higher, respectively, than those observed following

administration of TPIP 675 µg (C_{max} 717 pg/mL; AUC 5,480 pg*h/mL) (Laliberte et al., 2004). Minimal accumulation was observed following repeat doses of TPIP 225 µg QD for 7 days, and since a lower maximum dose (640 µg) will be used in the extended use portion of this study, TRE exposures are expected to be lower than those observed following single doses of TPIP 675 µg in Study INS1009-102.

Based on the findings above, the TPIP dose will range from 80 µg to 640 µg QD in this treatment period.

4.4. Study Completion

A participant will be considered to have completed the study if he/she has completed the Study Day 30 safety follow-up (shown in Table 1) and has not elected to enter the optional EUT period. A participant who has entered the optional EUT period will be considered to have completed the study if he/she has completed the EUT period safety follow-up (EUT Day 142). The study will be considered completed on the date of the last safety follow-up of the last participant in the study.

5. STUDY POPULATION

The study is expected to recruit approximately 6 to 10 participants at up to 12 centers with appropriate inpatient facilities. Eligible participants must have clinically stable disease of mild to moderate severity, with good to moderate functional status. Participants may not be taking more than 2 medications from the following classes:

- Endothelin receptor antagonists (eg ambrisentan, bosentan, macitentan),
- Phosphodiesterase type 5 inhibitors (eg sildenafil, tadalafil)
- Guanylate cyclase stimulator (eg riociguat)

It is expected that the site will recruit appropriate potential participants according to the criteria in Section 5.1 and Section 5.2.

The study inclusion and exclusion criteria include thresholds of selected RHC and ECG parameters that must be met at Baseline or the participant will not be considered eligible for the study. In this case, the participant is to be reported as a Screen Failure (Section 5.4).

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if they meet all of the following criteria[a]:

Age:
1. Participant must be ≥ 18 years of age at the time of signing the informed consent.
Type of Participant and Disease Characteristics
2. Participants must have a diagnosis of WHO Group 1 PH (PAH) with the following characteristics (Galie et al., 2016): a. Etiology of idiopathic, heritable, drug/toxin-induced or connective tissue disease (CTD)-related PAH; b. Right heart catheterization with the following hemodynamic findings: - Mean pulmonary arterial pressure (mPAP) > 20 mmHg at rest, - Pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg, and - Pulmonary vascular resistance (PVR) of ≥ 3 Wood Units (WU) 3. PAH diagnosis of at least 1 year 4. New York Heart Association (NYHA)/WHO Functional capacity Class I-III 5. No change in pulmonary hypertension medications (e.g., ambrisentan, bosentan, macitentan, sildenafil, tadalafil, riociguat) or dosage for at least 90 days prior to Screening. 6. No change in diuretic use or dosage for at least 30 days prior to Screening

7. Documented predicted percent forced vital capacity (FVC) > 70% within 1 year of Screening. If not available, pulmonary function testing will be performed at Screening (Table 1).
8. At least 2 of the following European Respiratory Society/European Society for Cardiology (ERS/ESC) low risk criteria:
    a. NT-pro-BNP concentration < 300 ng/L within 6 months of Baseline (if not available will be obtained at Screening, Table 1).
    b. Historical documentation of 6- minute walk distance (6MWD) > 440 meters within 6 months prior to Baseline. If not available will obtain 6MWD test at Screening (Table 1).
    c. Right atrial pressure (RAP) < 8 mmHg within 1 year prior to Baseline
    d. Cardiac Index (CI) ≥ 2.5 L/min*m^2 or mixed venous oxygen saturation (MVO_2) > 65% within 1 year prior to Baseline
9. Right heart catheterization at Baseline with the following hemodynamic findings:
    a. Mean pulmonary arterial pressure (mPAP) > 20 mmHg at rest,
    b. Pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg, and
    c. Pulmonary vascular resistance (PVR) of ≥ 3 Wood Units (WU)

Weight

10. Body mass index (BMI) within the range 18.0 - 32.0 kg/m^2 (inclusive).

Sex and Contraceptive/Barrier Requirements

11. Male participants: Male participants and their female partners of childbearing potential must agree to use highly effective contraception from Study Day 1 to at least 90 days after dosing.
12. Female participants: Women of child-bearing potential (WOCPB, defined as premenopausal, not surgically sterile for at least 3 months prior to Screening) must use a highly effective contraception method and agree to be tested for pregnancy from at Screening, Baseline, and 30 days after dosing.

See Section 10.4 for contraceptive guidance.

Informed Consent

13. Capable of giving signed informed consent as described in Section 10.1.5 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

[a] Please note that participants who enroll in the optional EUT period beyond the initial 30 day follow-up period will be screened to confirm that they still meet inclusion/exclusion criteria. Please refer to Table 5.

5.2. Exclusion Criteria

Participants are excluded from the study if they meet any of the following criteria[a]:

Medical Conditions

1. Any PH other than idiopathic, hereditary, drug/toxin-induced, or connective tissue disease (CTD) associated PAH (e.g., congenital heart disease-associated PAH, portal hypertension-associated PAH, PH belonging to Groups 2 through 5)
2. Allergy, or documented hypersensitivity or contraindication, to the ingredients of treprostinil palmitil inhalation powder (TPIP) or treprostinil (TRE).
3. Previous intolerance to prostacyclin analogs or receptor agonists (e.g., selexipag) per Investigator discretion
4. History of anaphylaxis or previously documented hypersensitivity reaction to any drug per Investigator discretion
5. QTcF interval > 480 ms on resting ECG at Baseline
6. History of heart disease including left ventricular ejection fraction (LVEF) ≤ 40% or clinically significant valvular, constrictive, or atherosclerotic heart disease (myocardial infarction, etc)
7. Abnormal renal function (estimated glomerular filtration rate < 30 mL/min/1.73m^2) at Screening.
8. Active liver disease or hepatic dysfunction manifested as:
    a. Elevated liver function test results (ALT or AST > 2 × ULN) at Screening
    b. Bilirubin > 1.5 × ULN (isolated bilirubin > 1.5 × ULN; ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%) at Screening.
    c. Known hepatic or biliary abnormalities, not including Gilbert's syndrome or asymptomatic gallstones at Screening.
9. History of HIV infection/positive HIV serology test result at Screening.
10. History of active/chronic Hepatitis B or C/ positive hepatitis B or C serology test result at Screening
11. History of abnormal bleeding or bruising.
12. Known or suspected immunodeficiency disorder, including history of invasive opportunistic infections (e.g., tuberculosis, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis) despite infection resolution, or otherwise recurrent infections of abnormal frequency, or prolonged infections suggesting an immune-compromised status, as judged by the Investigator.

13. Active and current symptomatic infection by SARS CoV 2. Additional COVID 19 restrictions per institutional guidelines (See also Section 10.1.3.1.3) 14. Participants with current or recent (past 4 weeks) lower respiratory tract infection (may be re-screened at appropriate time (Section 5.4) 15. History of malignancy in the past 5 years, with exception of completely treated in situ carcinoma of the cervix and completely treated non-metastatic squamous or basal cell carcinoma of the skin.
Concomitant Therapy
16. Participants receiving triple combination therapy for PAH consisting of endothelin receptor agonists, phosphoesterase type 5 inhibitors, and guanylate cyclase stimulators (riociguat). 17. Participants receiving prostanoids/prostacyclin agonists 18. Participants receiving potent CYP2C8 inhibitors, such as gemfibrozil 19. Other prior/concomitant therapies are allowed/disallowed at the Investigator's discretion
Prior/Concurrent Clinical Study Experience
20. Have participated in any other interventional clinical studies within 30 days of Baseline
Diagnostic assessments
21. Any clinically significant abnormal laboratory, value, test result, or physical examination finding at Screening; diseases or diagnoses/disorders that, in the opinion of the Investigator, may put the participant or others at risk by participating in the study, interfere with the participant's treatment and assessment, or influence the results of the study; or have compliance issues with the study.
Other Exclusions 22. Current or history of substance and/or alcohol abuse per Investigator assessment 23. Current user of cigarettes or e-cigarettes 24. Pregnant or breastfeeding.

[a] Please note that participants who enroll in the optional EUT period beyond the initial 30 day follow-up period will be screened to confirm that they still meet inclusion/exclusion criteria. Please refer to Table 5.

5.3. Lifestyle Considerations

No lifestyle restrictions are required.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study because they did not meet all inclusion criteria or meet one or more exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened twice at the Investigator's discretion. If a participant can be rescreened, the PI is to consult with the Medical Monitor to determine whether some or all of the screening assessments must be repeated. Rescreened participants will sign a new ICF and will be assigned a new participant number.

5.5. Criteria for Temporarily Delaying Inpatient Treatment Period

Following successful screening and meeting of study eligibility criteria, the inpatient treatment period and RHC procedure must be scheduled without delay.

The scheduled treatment period may be temporarily delayed no longer than 28 days by the Investigator in consultation with the Medical Monitor for valid reasons. Examples of valid reasons for delaying the treatment period may include such things as a life event for the participant (eg death in the family), local public health emergency (e.g., COVID 19 outbreak), site facility issues (e.g., catheterization lab or ICU bed availability), or pending TPIP dosing directives from the SRC.

A temporary delay in the scheduled inpatient treatment period for a valid reason may result in previously met Inclusion Criteria that rely on a time window to be not met (e.g., 6MWD falls outside the 6 months prior to Baseline window). This is not considered to be a Screen Failure. In this case, the Investigator should consult with the Medical Monitor to identify which screening tests need to be conducted or repeated to ensure that the participant meets study inclusion criteria and can safely participate in the study.

Deterioration of the participant's medical condition is not a valid reason to delay start of the inpatient treatment period. In some cases, delaying the inpatient treatment period may cause the participant to meet one or more exclusion criteria (e.g., participant develops a lower respiratory infection). In this case the participant should be considered a Screen Failure and Section 5.4 applies.

6. STUDY IMP AND CONCOMITANT THERAPY

Study IMP is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study IMP Administered

6.1.1. Inpatient Treatment Period (Single Dose)

A single dose of TPIP will be used in the inpatient treatment period, as listed below. A dose may consist of a single capsule or of multiple capsules administered in succession.

Name of Treatment	Dose	Supplied Formulation	Route and Frequency of Administration
Treprostinil palmitil inhalation powder (TPIP)	One or more single actuation capsules	Single actuation capsules containing 112.5 µg TP per 7.5 mg powder	Inhalation; single dose after Baseline assessments
Treprostinil palmitil inhalation powder (TPIP)	One or more actuation capsules (80 µg, 160 µg, 240 µg, 320 µg, 400 µg, 480 µg, or 640 µg)	Dry powder single actuation capsules containing 80 µg, 160 µg, or 320 µg	Inhalation; single dose after Baseline assessments

QD = once daily

6.1.2. Optional Extended Use Treatment Period

The IMP used in the EUT period will be capsules containing 1 of 3 dosage strengths of TPIP (80 µg, 160 µg, or 320 µg). IMP should be taken around the same time every day. Administration of IMP will be via inhalational dry powder packaged in single actuation capsules. One or 2 capsules will be administered for each dose. Administration of 2 capsules should be done sequentially. Each TPIP capsule contains 8 mg, 16 mg, or 32 mg of dry powder containing 80 µg, 160 µg, or 320 µg of the TP prodrug, respectively.

Name of Treatment	Dose	Supplied Formulation	Route of Administration
Treprostinil palmitil inhalation powder (TPIP)	One or two single actuation capsules (80 µg, 160 µg, 240 µg, 320 µg, 400 µg, 480 µg or 640 µg QD)	Dry powder single actuation capsules containing 80 µg, 160 µg, or 320 µg	Inhalation (QD)

QD = once daily

6.1.3. Medical Devices

In the planned clinical study, the TPIP will be administered by oral inhalation using a Plastiape capsule-based Dry Powder Inhaler (RS 01 Mod 7). A Type III Drug Master File is filed at the US FDA and the RS01 inhaler is classified as a Class I medical device. The Instructions for Use of the device document is provided separately as an Appendix to the Pharmacy Manual.

All device deficiencies (including malfunction, use error, and inadequate labeling) shall be documented and reported by the Investigator throughout the clinical investigation (Section 8.3.7) and appropriately managed by Insmed.

6.2. Preparation/Handling/Storage/Accountability

Insmed Incorporated will provide the Investigator and clinical unit with adequate quantities of TPIP capsules. For 112.5 µg doses, TPIP-filled HPMC capsules will be delivered in HDPE bottles overwrapped with an aluminum pouch, containing a sachet of desiccant to prevent moisture ingress. For 80 µg, 160 µg, and 320 µg doses, HDPE bottles will be closed with the desiccant placed inside the bottle, and induction sealed. The powder will be administered by oral inhalation using a Plastiape capsule-based Dry Powder Inhaler.

6.2.1. Inpatient Treatment Period (Single-dose)

Directions for preparation and administration of the TPIP dose to the participant are provided in a separate document as an Appendix to the Pharmacy Manual for the single-dose Inpatient Period.

All study IMP must be stored according to the labeled instructions in a secure cabinet or room with access restricted to necessary clinic personnel. The site will be required to keep a temperature log to establish a record of compliance with storage conditions. Current stability data supports the shelf life assigned to TPIP when stored at 2 to 8 °C.

- The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study IMP received and any discrepancies are reported and resolved before use of the study IMP.
- Only participants enrolled in the study may receive TPIP and only authorized site staff may supply or administer it. All TPIP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
- The Investigator, institution, and/or pharmacist or designee is responsible for study IMP and dosing devices accountability, reconciliation, and record maintenance (e.g., receipt, reconciliation, and final disposition records).
- Study IMP and dosing device accountability records will be maintained for all clinical supplies. All transactions will be recorded on the drug and dosing device accountability records including shipment receipts and study participant doses. All transactions will be recorded on a real-time basis.

- The Investigator/site will maintain detailed documentation of the number and identification of bottles and dispensing units of TPIP with copies of these documents to be provided to Insmed at the end of the study. All used and unused study IMP and dosing devices will be maintained by the site until inventoried by the study monitor. Upon completion of the study IMP and dosing device inventory by the study monitor, used and any unused study IMP and dosing devices will be disposed of in accordance with instructions provided to sites and according to site destruction policies. Documentation of destruction must be provided to Insmed.
- Further guidance and information for the final disposition of unused study IMP supplies can be obtained from Insmed.

6.2.2. Optional Extended Use Treatment Period

Directions for preparation and administration of IMP to the participant in-clinic are provided in the Pharmacy Manual for the optional EUT period. Directions for preparation and administration of IMP for home use will be provided to the participants.

Only participants enrolled in the study may receive IMP, and only authorized study personnel may supply IMP. All IMP must be stored according to the labeled instructions with access restricted to necessary clinic personnel. The site will be required to keep a temperature log to establish a record of compliance with storage conditions. Refer to the Pharmacy Manual for the optional EUT period for shelf-life and storage conditions.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for IMP and dosing devices accountability, reconciliation, and record maintenance (e.g., receipt, reconciliation, and final disposition records). Directions for storage, handling, accountability, and destruction are provided in the Pharmacy Manual for the optional EUT.

6.3. Measures to Minimize Bias: Randomization and Blinding

Not applicable.

6.4. Study Intervention Compliance

6.4.1. Inpatient Treatment Period (Single Dose)

Study participants will receive the TPIP dose directly from the Investigator or designee, under medical supervision, in an appropriate inpatient setting. The date and time of the dose administered will be recorded in the source documents. The dose of TPIP and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the TPIP.

6.4.2. Optional Extended Use Treatment Period

At each in-clinic visit, participants will be dispensed adequate IMP to allow for daily dosing. When participants are dosed at the site, IMP administration will be overseen by study site personnel. The date and time of each dose self-administered in the clinic will be recorded in the

source documents. The dose of IMP and study participant identification will be confirmed at the time of dosing by a member of the study site personnel.

When participants administer IMP at home, compliance with IMP will be assessed at each in-clinic visit. Participants will record their daily dose on paper dosing diaries. Compliance will be assessed by direct questioning, review of participant dosing diaries, and counting of returned capsules during the site visits. Participants will return unused capsules and used study capsules and devices to the study site at each in-clinic visit. Participants who undergo a study drug taper will return unused capsules and used capsules and devices to the study site at a follow-up visit. Unused capsules should be returned in the bottle they were dispensed in. Deviation(s) from the prescribed dosage regimen should be recorded.

A record of the quantity of capsules dispensed to and administered by each participant must be maintained and reconciled with study drug logs and participant dosing diaries. Study drug start and stop dates, including dates for study drug interruptions and/or dose reductions will also be recorded.

6.5. Dose Modification

Dose modification is part of the study design and is described in detail in Section 4.3 and Section 1.3.2.

6.6. Continued Access to Study Intervention After the End of the Study

Not applicable.

6.7. Treatment of Overdose

An overdose is defined as the participant receiving any TPIP in excess of their assigned dose as predetermined by the SRC (Section 4.3). An overdose itself is not an AE. However, if the overdose results in clinical signs and symptoms, it requires expedited reporting as if it is an SAE. The Investigators must refer to the relevant documents for detailed information regarding warnings, precautions, contraindications, AEs, and other significant data pertaining to the study IMP. Such documents may include, but are not limited to, the Investigator's brochure.

In the event of an overdose, the Investigator must:

- Contact the Medical Monitor within 24 hours.
- Evaluate the participant to determine, in consultation with the Medical Monitor, how to proceed with treatment period procedures and assessments.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until TP or TRE is likely to be sufficiently metabolized and/or excreted and/or can no longer be detected systemically. The frequency and duration of plasma sampling from the last dose of TPIP must be determined by the Investigator in conjunction with the study team and Medical Monitor.
- The overdose must be fully documented (e.g., quantity of the excess dose, duration of the overdose, how it happened) in the CRF.

6.8. Concomitant Therapy

Any medications, treatments, or therapies that the participant is receiving at Baseline (Study Day 1) or receives during the study (Study Day 1 through end of study [EOS]) are considered concomitant therapy and will be collected and documented in the study CRF.

Documentation includes the name of the therapy, with the reason for use, the dates of administration including start and end dates, and dosage information including dose and frequency.

Prior medications are those medications taken before the first dose of study IMP. A medication that starts prior to first dose but continues after the first dose of study IMP is classified both in prior and concomitant medications. Any procedures performed from Day 1 through EOS are considered concomitant procedures and will be collected and documented in the study CRF.

The Medical Monitor must be contacted if there are any questions regarding concomitant or prior therapy.

For participants who enroll in the EUT period, new concomitant therapy for the period from the single-dose Study Day 30 follow-up until the enrollment in the EUT will be collected during participant's screening for the EUT.

7. DISCONTINUATION OF STUDY IMP AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study IMP

7.1.1. Single-dose Period

This is a single dose period; not applicable.

7.1.2. Optional Extended Use Treatment Period

If study drug is permanently discontinued, the participant will be encouraged to participate in their remaining study visits. See Table 6 for data to be collected at the time of discontinuation of IMP and follow-up. If a participant discontinues the study and needs to be started on another PAH medication, the Investigator should contact the Medical Monitor.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons.

At the time of discontinuing from the study after study drug administration, if possible, an early discontinuation evaluation should be conducted to maximize participant safety. This final evaluation and the reason for participant withdrawal must be documented in the CRF.

The participant will be permanently discontinued both from the study drug and from the study at that time.

If the participant is discontinued from the study due to an SAE, the Investigator will follow the participant until the Investigator deems that the SAE has resolved or stabilized.

The Investigator may withdraw the participant from the study due to absence of a PD response to TPIP. Lack of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the PK and PD assessments.

If the participant withdraws consent for disclosure of future information, Insmed may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled follow-up visits and is unable to be contacted by the study site.
The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of

maintaining the assigned visit schedule and ascertain whether or not the participant wishes to continue in the study.

- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts must be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered lost to follow-up and to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants, including those who did not get study IMP. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Insmed personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1.13.2).

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in Table 1, Table 2, Table 3, Table 4, Table 5, Table 6.

All screening evaluations must be completed and reviewed to confirm that potential participants meet eligibility criteria prior to scheduling the study RHC procedure and inpatient admission. The RHC procedure and inpatient admission must be scheduled for as soon as possible once the participant's eligibility for the study is confirmed by screening. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (e.g., previous RHC, previous echocardiogram, previous 6MWD test) and obtained before signing of the ICF may be utilized for screening or Baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frames defined in the inclusion and exclusion criteria in Section 5.

For participants who do not elect to enter the EUT period, the maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required is expected to be approximately 140 mL and will not exceed 200 mL. Approximately 80 mL will be required for PK sampling over 48 hours and approximately 20 mL for biomarker sampling. Safety and screening blood samples will require approximately 20 to 30 mL. Blood loss from the RHC procedure is anticipated to be negligible.

For participants who do elect to enter the optional EUT period within the 30 day follow-up window in the single-dose period, there is no anticipated blood collection. For participants who elect to enter the optional EUT period after the 30 day follow-up in the single-dose period, Safety and screening blood samples will require approximately 20 to 30 mL. Blood loss from the RHC procedures is anticipated to be negligible.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples at the Investigator's discretion.

At any time, the Investigator has the option to discontinue assessments for participant safety or tolerability reasons. Additional laboratory, PK, and/or hemodynamic assessments may be performed as deemed necessary for participant safety. Following completion of scheduled events, the Investigator has the option of continued laboratory and/or hemodynamic monitoring as deemed appropriate for participant safety. If, in the interest of participant safety, the Investigator omits scheduled assessments/procedures or performs additional assessments/procedures, the reason for doing so must be reported on the CRF as an AE in order to avoid a protocol violation.

8.1. Pharmacodynamic Assessments

The results of each individual participant's PD assessments will contribute to the dosing decision for the next participant (Section 4.3).

8.1.1. Required PD Assessments with RHC

PVR, CO, PAP (mean), RAP (mean), RVP, hemoglobin, and MVO_2 will be measured via the RHC at the time points indicated in the SoA (Table 2). Oxygen consumption is part of the MVO_2 calculation and may be measured or estimated at 125 mL O_2 per square meter (m^2) of body surface area (BSA). These or other parameters may be optionally measured at other time points or omitted to ensure participant safety at the Investigator's discretion. If measurements are missed, or additional measurements are taken for safety purposes, the reason must be documented as an AE in the CRF.

Institutional procedures for insertion, care, monitoring, and removal of the RHC will be followed. Specific technique and procedures for measurement of PVR, CO, PAP, RAP, RVP, hemoglobin, oxygen consumption, and MVO_2 are provided in a separate Procedure Guide.

8.1.2. Required Non-invasive PD Assessments

Systemic blood pressure (mmHg) may be measured by inflatable cuff. Systemic blood pressure must include 3 values: systolic, diastolic, and mean arterial pressure. Arterial oxygen saturation (SpO_2, %) and heart rate (beats per minute) may be measured by pulse oximeter.

8.1.3. Resting Respiratory Gas Exchange Assessments

Specific measurements for resting respiratory gas exchange assessment include changes from Baseline in respiratory rate (breaths per minute), minute ventilation (mL per minute), carbon dioxide production (VCO_2, mL per minute), end tidal oxygen concentration (ETO_2, %), and end tidal carbon dioxide concentration ($ETCO_2$, %). The gas exchange parameters will be monitored at the same time points as the PD assessments in Section 8.1.1 (Table 2, Table 4). Specific instructions for resting respiratory gas exchange assessment procedures and measurements are provided in a separate Procedure Guide.

8.1.4. Transthoracic Echocardiogram Assessments

Transthoracic echocardiogram is to be performed at Baseline and during a 2-8 hour window following TPIP administration (Table 4). Specific instructions for echocardiographic procedures and measurements are provided in a separate Procedure Guide.

8.1.5. Pulmonary CT Scan

8.1.5.1. Single-dose Period

Pulmonary CT scanning to assess pulmonary vasculature and blood flow is scheduled for Baseline and during a 4-8 hour window following TPIP administration (Table 4). Specific requirements and instructions for pulmonary CT scanning and required parameters are provided in a separate Procedure Guide.

8.1.5.2. Optional Extended Use Treatment Period

An optional pulmonary CT scan may be performed at first visit (±3 days) and at EUT Week 16 (±3 days) in the optional EUT period, as indicated in Table 6. The CT scan will be performed according to instructions provided by the CT scan vendor.

8.2. Safety Assessments

Evaluation of the safety and tolerability of single doses of TPIP in participants with PAH is the primary objective of this study. Planned time points for all safety assessments are provided in Table 1 and Table 2. The results of the individual participant's safety assessments during and after TPIP administration will contribute to the dosing decision for the next participant (Section 1.3.2). Participants who elect to enter the optional EUT period will also be monitored for safety, as listed in Table 6.

8.2.1. Physical Examinations

Screening: The physical examination must focus on those areas that determine the individual participant's eligibility to participate in the study and do so safely at the Investigator's discretion and will be documented accordingly.

Baseline: The physical examination must focus on the participant's fitness for the study procedures and TPIP administration.

Discharge: The physical examination must focus on the participant's fitness to be safely discharged to home from the inpatient setting. Special attention must be paid to assessment of any new or ongoing AEs.

Follow-up: The in-person physical examination must focus on participant safety and assessment of AEs that were ongoing at discharge or have occurred since discharge.

8.2.2. Vital Signs

8.2.2.1. Single-dose Period

Temperature, heart rate, respiratory rate, and blood pressure at screening and 48 hour post-TPIP administration follow-up will be per the Investigator's usual outpatient practice and documented accordingly.

Baseline and post-TPIP administration: Changes from Baseline in heart rate, respiratory rate, and systemic blood pressure are PD endpoints as well as safety variables and must be measured as specified (Section 8.1). Vital signs outside of PD endpoints will be monitored per the inpatient unit's usual practices.

8.2.2.2. Optional Extended Use Treatment Period

Changes in heart rate, respiratory rate, body temperature, and systemic blood pressure will be monitored as described in Table 6. Vital signs will be measured at Extended Use

Screening/Baseline (EUT Day 1), EUT Week 2, EUT Week 3, EUT Week 5, EUT Week 10, and EUT Week 16 and at the Early Discontinuation visit, if appropriate.

8.2.3. Electrocardiograms

Screening: a single 12-lead ECG will be conducted per the Investigator's usual practice

Baseline: A single 12-lead ECG will be performed to ensure the participant's eligibility for the study (Section 5.2). Inpatient telemetry monitoring will be utilized per the unit's usual practice until the participant is discharged from the inpatient setting, but routine telemetry readings will not be collected as study data unless they pertain to a relevant AE.

48 hours post-TPIP administration follow-up: a single 12-lead ECG will be conducted per the Investigator's usual practice.

8.2.4. Clinical Safety Laboratory Assessments

See Section 10.2 (Table 7) for the list of clinical laboratory tests to be performed and the SoA (Table 1, Table 2, Table 5, Table 6) for the timing and frequency. All clinical laboratory tests will be performed locally by the study site.

The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the Investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 7 days after TPIP dosing must be repeated at the Investigator's discretion, consistent with the participant's level of disease until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

- If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology must be identified, and Insmed notified.]
- All protocol-required laboratory tests, as defined in Section 10, Appendix 2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.4).
- If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose modification), then the results must be recorded.

8.2.5. Pregnancy Testing

8.2.5.1. Single-dose Period

Willingness of WOCBP to undergo serum or urine pregnancy testing is a study eligibility criterion. Pregnancy tests will be conducted at screening, baseline, and Study Day 30. WOCBP

participants will be provided a home pregnancy test kit with instructions to conduct and report test results at the Study Day 30 follow-up visit which is scheduled to be by telephone call or telemedicine. If the participant elects to enter the optional EUT period and the remote safety follow-up visit overlaps with the start of the EUT period, the results of a urine pregnancy test will be recorded at the first visit in the extended treatment period.

8.2.5.2. Optional Extended Use Treatment Period

Urine pregnancy tests will be performed in-clinic at EUT Baseline (EUT Day 1) in WOCBP. WOCBP participants will be provided home pregnancy test kits with instructions to conduct the pregnancy tests every 30 days or more if required during the treatment and follow-up periods. Study site personnel will contact the participant every 30 days by telephone and record the pregnancy test results. An additional on-site urine test must be performed prior to starting any procedure that requires the use of ionizing radiation.

8.3. Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

The definitions of AEs and SAEs can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative). AEs may be solicited or unsolicited. Solicited and unsolicited AEs are defined in Section 10.3.

The Investigator is responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE as provided in the protocol and remain responsible for following up all AEs.

The Investigator should proactively follow participants with AEs until the EOS for each participant. At the EOS visit, the Investigator will record the AE status (stable or not stable) in the electronic CRF.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs (serious and non-serious) for the core, single-dose period will be collected from the signing of the ICF until the Study Day 30 follow-up visit at the time points specified in the SoA (Table 1, Table 2). Medical occurrences that begin after obtaining informed consent but before TPIP administration will be recorded as Medical History/Current Medical Conditions, not as AEs.

SAEs that occur after signing the ICF but before study IMP starts must be recorded and reported as SAEs. Non-serious medical occurrences that begin after obtaining informed consent but before TPIP administration will be recorded as Medical History/Current Medical Conditions, not as AEs.

For participants who enroll in the EUT period, AEs for the period from the single-dose Study Day 30 follow-up until the enrollment in the EUT will be collected during participant's screening for the optional EUT period. All AEs and SAEs for participants who choose to enroll in the optional EUT period will be recorded at the time points specified in the SoA (Table 5, Table 6).

All SAEs will be recorded and reported to Insmed or designee immediately and under no circumstance must this exceed 24 hours, as indicated in Appendix 3, (Section 10.3). The Investigator will submit any updated SAE data to Insmed within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study IMP or study participation, the Investigator must promptly notify Insmed.

8.3.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. The Investigator should proactively follow participants with AEs until the EOS for each participant. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline due to study completion, then the site can report this information to the Medical Monitor by email or telephone.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to Insmed of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

Insmed has a legal responsibility to notify relevant health authorities and regulatory agencies about the safety of a study drug under clinical investigation. This study is being conducted in the USA only; regulatory requirements relating to safety reporting to the US FDA, IRBs, and investigators will be followed.

An Investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from Insmed will review and then file it along with other study documents and will notify the IRB, if appropriate according to local requirements.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Insmed policy and forwarded to Investigators as necessary. No serious adverse

reactions are considered expected for TPIP. Please refer to the Reference Safety Information in Section 6.1 of the Investigator's Brochure.

8.3.5. Pregnancy

Details of all pregnancies that occur in WOCBP participants within 30 days after TPIP administration will be collected. Male participants with WOCBP partners must continue to use contraception for 90 days after TPIP administration and report any pregnancies that occur within that time period.

If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to Insmed within 24 hours of learning of the pregnancy in a female participant or female partner of male participant and after obtaining the necessary signed informed consent from the female partner.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

Any female participant who becomes pregnant while participating in the study will be discontinued from the study.

8.3.6. Adverse Events of Special Interest (AESI)

There are no AESIs for TPIP that require special collection and rapid communication by the Investigator.

8.3.7. Medical Device Deficiencies

A medical device, the Plastiape capsule based Dry Powder Inhaler is being provided for use in this study to administer TPIP. To fulfill regulatory reporting obligations worldwide, the Investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a Medical Device deficiency and reporting requirements and procedures for device deficiencies and AEs/SAEs resulting from device deficiencies can be found in Section 10.6.

8.3.7.1. Time Period for Detecting Medical Device Deficiencies

- Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the Investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such a deficiency is considered reasonably related to a medical device provided for the study, the Investigator will promptly notify Insmed.

The method of documenting Medical Device Deficiency is provided in Section 10.6.

8.3.7.2. Follow-Up of Medical Device Deficiencies

Follow-up applies to all participants who experienced a device deficiency.

The Investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.

New or updated information will be recorded on the originally completed form with all changes signed and dated by the Investigator.

8.3.7.3. Prompt Reporting of Device Deficiencies to Insmed

Device deficiencies will be reported to Insmed within 24 hours after the Investigator determines that the event meets the protocol definition of a medical device deficiency.

8.3.7.4. Regulatory Reporting Requirements for Device Deficiencies

The Investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for Insmed to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The Investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB.

8.4. Pharmacokinetic Assessments

The schedule for PK assessments and sampling windows during the single-dose period is shown in Table 3. The 48 (± 4) hour post-TPIP administration blood draw is expected to be done on an outpatient basis.

8.4.1. PK Sample Collection

Plasma blood samples of approximately 10 mL each will be collected for measurement of plasma concentrations of TP and TRE as specified in the SoA (Section 1.4).

A maximum of 2 samples may be collected at additional time points during the study if an SAE occurs or at early termination.

Each PK plasma sample will be divided into 2 aliquots (1 each for PK analysis and the other for backup. All samples will be stored frozen (-70°C or -20°C) until shipment and then stored at -70°C until analysis. The actual date and time (24-hour clock time) of each sample will be recorded.

Full instructions for the collection and handling of PK samples will be provided by Insmed in a separate Laboratory Manual.

8.4.2. PK Analysis

Individual PK parameters of TRE and TP will be determined using non-compartmental analysis for the following parameters: C_{max}, t_{max}, $AUC_{t1–t2}$, $AUC_{0–\infty}$, CL/F, Vd/F, and $t_{1/2}$.

8.4.3. Pharmacokinetic and Pharmacodynamic Evaluations

Relationships between PK (TP dose and TRE exposure) and PD effects and safety will be explored and reported separately.

8.5. Genetics / Pharmacogenomics

Genetic and/or pharmacogenomic analyses are not included in this study.

8.6. Biomarkers

A blood sample for NT-pro-BNP will be taken at screening if needed as part of study inclusion criteria (Section 5.1).

Blood samples (5-7 mL per time point) will be collected for biomarker measurement at Baseline and at 4 and 8 hours after TPIP administration. The plasma generated from the blood samples will be stored frozen (-70 C or lower is preferred) until shipment and analysis.

Full instructions for the collection and handling of biomarker samples will be provided by Insmed in a separate Laboratory Manual.

8.7. Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

8.8. Immunogenicity Assessments

Immunogenicity assessments do not apply to this study of a small molecule.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

No statistical hypotheses will be evaluated in this study.

9.2. Sample Size Determination

The sample size for this study is not based on statistical power calculations. The planned number of evaluable participants to complete the study is approximately 6-10.

9.3. Analysis Sets

The analysis sets comprise participants who are considered evaluable for the parameters under consideration.

All participants who receive a single dose of TPIP will be considered evaluable for safety and included in the safety population.

All participants who receive a single dose of TPIP and have a least one measurable post-dose plasma TP/TRE concentration will be considered evaluable for PK and included in the PK population.

All participants who receive a single dose of TPIP and have a Baseline datapoint and at least one measurable post-dose PD datapoint will be considered evaluable for PD and included in the PD population.

All participants who receive a single dose of TPIP and have at least 1 measurable post-dose biomarker datapoint will be considered evaluable for biomarkers and included in the biomarker population.

9.4. Statistical Analyses

The statistical analysis plan will be finalized prior to Database Lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

There is no hypothesis-testing in this study and no inferential statistical analyses will be conducted. There will be no proxy values for missing data. Participant PK, PD, and biomarker data will be presented individually in listings and graphs as appropriate for each variable.

The frequency of TEAEs is the primary endpoint for this study. All safety analyses will be performed on the safety population. AE listings as required by ICH E3 guidelines will be produced. TEAEs, SAEs, AEs leading to treatment and/or study withdrawal, and AESIs will be listed for each participant along with outcome, severity, and relatedness to study IMP. Ad hoc summaries of TEAEs may be prepared if the volume of data allow.

PK and PD values for secondary endpoints will be listed and graphed if appropriate for each evaluable participant.

PK and PD values for exploratory endpoints will be listed and graphed as appropriate for each participant.

9.4.2. ECG, Vital Signs, Clinical Laboratory Values

ECG data will be listed for each participant. Vital signs data that are not considered part of a PD assessment (Section 8.1) will be listed for each participant. Clinical laboratory values will be listed for each participant.

9.5. Interim Analysis

All available safety, PK, and PD data from each participant will be evaluated by the SRC prior to the next participant in order to determine the value of proceeding with the study and the TPIP dose for each subsequent participant (Section 4.3).

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

a. Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
b. Applicable ICH Good Clinical Practice (GCP) Guidelines
c. Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, Instructions for Use of the Plastiape capsule based Dry Powder Inhaler, and other relevant documents must be submitted to an IRB by the Investigator and reviewed and approved by the IRB before the study is initiated.

Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

d. Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
e. Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures
f. Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB, and all other applicable local regulations

10.1.2. Protocol Deviations

The Investigator must conduct the study in compliance with the protocol as agreed to by Insmed and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRB.

The Investigator must notify the IRB of deviations from the protocol in accordance with IRB reporting requirements.

As of May 2020, due to concern regarding COVID-19, there may be restrictions to participant attendance at in-clinic visits or elective inpatient admissions. In the event participants are restricted to attend in-clinic visits, or if the participant has concern regarding travel and attending in-clinic visits (due to potential public health concerns), the site must contact Insmed on how to

conduct the scheduled assessments, and decisions must be documented in the source documentation. Where necessary, in-clinic visits may be conducted via telemedicine link and home health care visits.

10.1.3. Public Health Emergency Situations

During the COVID-19 public health emergency, Insmed, IRBs, and Investigators shall follow the most current version of local guidance to assure the safety of study participants, maintain compliance with GCP, and minimize risks to study integrity. The continuity of clinical study conduct and oversight may require implementation of temporary or alternative mechanisms, which will remain in effect only for the duration of the local public health emergency. Examples of such mechanisms may include, but are not limited to, any of the following: telephone contact, virtual visits, telemedicine visits, online meetings, non-invasive remote monitoring devices, use of local clinic or laboratory locations, and home visits by skilled staff. The site must contact Insmed on how and when to implement temporary and/or alternative mechanism of scheduled assessments, and all decisions taken must be documented in the source documentation. Additionally, all temporary mechanisms utilized, and the resulting deviations from planned study procedures are to be documented as being related to COVID-19.

In a situation where local health authorities declare a public health emergency while the study is ongoing, the suggested guidance in the following subsections must be followed.

10.1.3.1. Continuation or Suspension of the Study

Ensuring the safety of trial participants is paramount. Insmed (Insmed Incorporated), in consultation with clinical Investigators and IRB, will determine if the protection of a participant's safety, welfare, and rights are best served by continuing or stopping the trial at the specific site. Such decision will depend on specific circumstances, including the ability to conduct appropriate safety monitoring, the potential impact on the investigational product supply chain, and other considerations.

If the decision is to continue the study, the following considerations will be taken into account:

10.1.3.1.1. Study Recruitment

Insmed will communicate to the sites the decision on whether to continue or suspend recruitment after considering the specific circumstances of each site, recommendation by the IRB, and its local health authority mandates. If, due to COVID-19, study discontinuation exceeds the assumed rate, Insmed may allow enrollment past the assumed sample size.

10.1.3.1.2. Participants Already Enrolled in the Study

If the decision is to continue the participation of participants already enrolled, the following steps must be taken:

- If a participant is not able to complete a protocol specified study visit, it may be necessary to adjust the visit schedule, convert in-clinic visits to telemedicine visits, and/or postpone study procedures until the next available in-clinic study visit. If there is information available from previous visits (e.g., laboratory assessments) that

requires follow-up procedures or other safety assessments, the Investigator will decide if an on-site visit or home healthcare visit is required or whether the participant's safety can be preserved by other means.

10.1.3.1.3. Participants Infected by COVID-19

If a participant has had a past documented mild to moderate COVID-19 infection prior to enrollment in the trial but the participant has recovered and the current diagnostic tests are negative (negative antigen by any diagnostic laboratory kit), the participant can be screened, at the Investigator's discretion. Participants who experienced hospitalization, severe disease, and/or COVID-19 acute respiratory distress syndrome (ARDS) must be excluded.

If a participant has a documented infection by COVID-19 while in the trial, the event will be reported as an AE or SAE, depending on the criteria. The Investigator will follow the guidance provided by health authorities in the treatment of those participants.

10.1.4. Financial Disclosure

The disclosed financial interest of the Investigator/sub-investigator must be collected before screening of the first participant, following study completion at the Investigator site and 1 year following overall study completion. The Investigator/sub-investigator must promptly update this information if any relevant changes occur during this period.

10.1.5. Informed Consent Process

Before a participant's participation in the study, it is the Investigator's responsibility to obtain freely given consent, in writing, from the participant or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any study IMPs are administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective participant, to the participant's participation in the clinical study. An informed consent document that includes both information about the study and the consent form will be prepared and given to the participant. This document will contain all the elements required by the ICH E6 (R2) Guideline for GCP and any additional elements required by local regulations. The written ICF must be prepared in the local language(s) of the potential participant population.

In obtaining and documenting informed consent, the Investigator must comply with the applicable regulatory requirements, and must adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form and any revision(s) must be approved by the IRB prior to being provided to potential participants.

The participant's written informed consent (written or electronic) must be obtained prior to his/her participation in the study, and must be documented in the participant's medical records, as required by applicable regulations. The ICF must be signed and personally dated by the participant or a legally acceptable representative, and by the person who conducted the informed consent discussion (not necessarily the Investigator). The signed ICF must be retained in accordance with institutional policy, and a copy of the signed consent form must be provided to

the participant or legal representative. The date and time that informed consent was given must be recorded in the CRF.
Participants who are rescreened are required to sign a new ICF.

10.1.6. Protection of Participant Identification and Confidentiality

The Investigators and Insmed will preserve the confidentiality of all participants taking part in the study, in accordance with GCP and local regulations.

The Investigator must ensure that the participant's anonymity is maintained. On the CRF or other documents submitted to Insmed, participants must be identified by a unique participant identifier as designated by Insmed. Documents that are not for submission to Insmed (e.g., signed ICFs) must be kept in strict confidence by the Investigator.

In compliance with ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB direct access to review the participant's original medical records for verification of study-related procedures and data. The Investigator is obligated to inform the participant that his/her study-related records will be reviewed by the above-named representatives without violating the confidentiality of the participant.

Participant names will not be supplied to Insmed. A participant number will be recorded in the CRF, and if the participant name appears on any other document (e.g., laboratory report), it must be obliterated on the copy of the document to be supplied to Insmed. All records will be kept confidential to the extent provided by federal, state, and local laws. The participants will be informed that representatives of Insmed, IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

The Investigator will maintain a personal participant identification list (participant numbers with the corresponding participant names) to enable records to be identified.

10.1.7. Committee Structure

An SRC will be responsible for monitoring safety data. The SRC will comprise all Investigators and key members of the Insmed Study Team (including but not limited to Medical Monitor, Medical Director(s), Safety/Pharmacovigilance Physician, Statistician, Clinical Pharmacologist) and external expert consultants. The SRC will continuously monitor all available safety, PD and PK data for each participant and will obtain consensus regarding the safety of continuing the study, the next TPIP dose, and clinical care of the next participant. Expert consultants may be invited to review and interpret participant data. With any safety findings, a decision will be made, based on the review, as to whether enrollment in the study will be allowed to continue. Decisions regarding final database values for PD parameters may be adjudicated by the SRC.

10.1.8. Dissemination of Clinical Study Data

Insmed will provide study information for inclusion in national registries according to national/local regulatory requirements.

Results of this study will be disclosed according to the relevant national regulatory requirements.

10.1.9. Data Quality Assurance

The Investigator/investigational site will permit study-related monitoring, audits, IRB review and regulatory inspections by providing direct access to source data/documents. Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of a clinical study.

10.1.9.1. Data Collection

All data obtained for this study will be entered into a 21 CFR Part 11 compliant Data Management System provided by Insmed or its designee. These data will be recorded with an EDC system using CRFs. The Investigator will ensure the accuracy and completeness of the data reported to Insmed. All data entry, modification or deletion will be recorded automatically in an electronic audit trail.

The Investigator will provide access to his/her original records to permit a representative from Insmed to verify the proper transcription of data. Data reported in the CRFs must be consistent with and substantiated by the participant's medical record and original source documents. The CRF data will be monitored by Insmed or designee. The final, completed CRF Casebook for each participant must be electronically signed and dated by the PI within the EDC system to signify that the Investigator has reviewed the CRF and certifies it to be complete and accurate.

Insmed will retain the final CRF data and audit trail. A copy of all completed CRFs will be provided to the Investigator.

10.1.9.2. Study Monitoring

Before study initiation, at a site initiation visit or at an Investigator's meeting, an Insmed representative will review the protocol, CRF, Investigator Brochure, and any study-related materials with the Investigators and their staff. During the study, Insmed study monitor or its designee will visit the site regularly to check the completeness of participant records, the accuracy of entries on the CRFs, adherence to the protocol, adherence to ICH GCP and applicable regulatory requirements, the progress of enrollment, and also to ensure that study IMP is being stored, dispensed, and accounted for according to specifications.

The Investigator must give the monitor access to relevant hospital or clinical records to confirm their consistency with the CRF entries. Participant confidentiality will be maintained by the study center. Insmed monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of primary activity and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study specific monitoring plan.

10.1.9.3. Audits and Inspections

Domestic and foreign regulatory authorities, the IRB, and an auditor authorized by Insmed may request access to all source documents, CRFs, and other study documentation for onsite audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must

provide support at all times for these activities. Medical records and other study documents may be copied during audit or inspection provided that participant names are obliterated on the copies to ensure confidentiality.

If an inspection is requested by a regulatory authority, the Investigator will inform Insmed, immediately that this request has been made.

10.1.9.4. Study Record Retention

Study documents must be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents must be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of Insmed. It is the responsibility of Insmed to inform the Investigator when these documents no longer need to be retained.

10.1.9.5. Source Documents

Source documentation is the point of initial recording of a piece of data. Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.10. Study Files and Materials

Before the start of any study related procedures, all initial documents required by ICH GCP, Good Pharmacoepidemiology Practice, and applicable local regulations must be available in the relevant files maintained by Insmed (or delegate) and the Investigator. An Investigator Study File prepared by Insmed (or delegate), containing all applicable documents for use at the study site, will be made available to the Investigator before the start of the study. A list of personnel and organizations responsible for conduct of the study as well as the list of Investigator-delegates (e.g., sub-investigator) at each site will be included in the Investigator Study File. The respective files will be kept and updated by Insmed (or delegate) and the Investigator, as applicable.

All study documentation and materials maintained in the Investigator Study File at the study site must be available for inspection by Insmed's study monitor (or delegate) to determine that all required documentation is present and correct.

The study may be audited by qualified delegates from Insmed or a competent regulatory authority.

10.1.11. Use of Stored Samples and Data

Stored samples will be labeled with study and participant information and secured with limited access and retained per protocol requirements and in accordance with the laboratory's operating procedures. Electronic data will be kept in password protected computers at the laboratory and then transferred to Insmed or CRO, as applicable, for data analysis. Samples and corresponding data will be tracked using the laboratory's specimen tracking system.

Prior Insmed and IRB approval are required before using or sharing study samples or data in ways not specifically specified in the study protocol during conduct of this study.

Any loss or unanticipated destruction of samples (e.g., freezer malfunction) or data (e.g., loss of a data sheet with individually identifiable information) that violates or compromises the scientific integrity of study data must be reported to Insmed and the IRB.

At any time, participants may inform the Investigator in writing that they do not wish to have their samples stored beyond the completion (termination) of the study. In this case, the Investigator will request that all known remaining samples be destroyed and report the disposition of samples to the requesting participants and the IRB.

10.1.12. Disposition of Stored Samples and Data

Participant samples will be secured with limited access and retained per protocol requirements and in accordance with the laboratory's operating procedures. Samples stored by the central laboratories will be labeled with the participant's study identification information. Data will be kept in password protected computers at the laboratory and then transferred to the vendor for data analysis. Samples and corresponding data acquired will be tracked using the laboratory's specimen tracking system.

In the future, if other Investigators may wish to study these samples and/or data, they need to obtain Insmed approval and participant consent before any sharing of samples and/or data.

Any loss or unanticipated destruction of samples (e.g., due to freezer malfunction) or data (e.g., loss of a data sheet with individually identifiable information) that results in a violation that compromises the scientific integrity of the data collected for the study will be reported to Insmed and the IRB.

Additionally, participants may withdraw authorization in writing to decline their sample storage for a period of up to 2 years beyond the duration of the study. In this case, the PI will request the destruction of all known remaining samples and report what was done to both the participant and to the IRB. This decision will not affect the individual's participation in the study.

10.1.13. Study and Site Start and Closure

Before the start of the study at each study site, Insmed's study monitor (or delegate) shall confirm adequacy of the facilities by study site visit or other acceptable methods.

The Investigator may not enroll any participant into the study before Insmed has received written approval or a favorable opinion from the IRB for conducting the study and a formal meeting has been conducted by Insmed's study monitor (or delegate) to initiate the study. This meeting will include a detailed review of the study plan, and completion of the CRF.

10.1.13.1. First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants. The first participant screened for participation in the study is considered the first act of recruitment.

10.1.13.2. Study/Site Termination

Insmed or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of Insmed. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.
The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.
Reasons for the early closure of a study site by Insmed or Investigator may include but are not limited to:
For study termination:

- Discontinuation of further study IMP development

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB or local health authorities, Insmed's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, Insmed shall promptly inform the Investigators, the IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and must assure appropriate participant therapy and/or follow-up.

10.1.14. Protocol Amendments

Any substantial change or addition to this protocol requires a written protocol amendment that must be approved by Insmed, before implementation. Amendments significantly affecting the safety of participants, the scope of the investigation, or the scientific quality of the study, require additional approval by the applicable regulatory authority(ies) and IRBs. Copies of the applicable written approvals must be filed in Insmed files and investigator site files.

The requirements for approval must in no way prevent any immediate action from being taken by the Investigator or by Insmed in the interests of preserving the safety of all participants included in the study. If an immediate change to the protocol is felt to be necessary by the Investigator and is implemented by him/her for safety reasons, Insmed or its agent must be notified and the applicable regulatory authority(ies)/IRBs must be informed as soon as possible. Any other regional reporting requirements must be adhered to.

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or regulatory authority/IRB approval, but the regulatory authority(ies)/IRBs must be kept informed of such administrative changes in accordance with country specific requirements.

10.1.15. Financing and Insurance

10.1.15.1. Finances

Prior to starting the study, the Investigator and/or institution will sign a clinical study agreement with Insmed. This agreement will include the financial information agreed upon by the parties.

10.1.15.2. Reimbursement, Indemnity, and Insurance

Reimbursement, indemnity, and insurance shall be addressed in a separate agreement on terms agreed upon by the parties.

10.1.15.3. Participant Reimbursement, Liability and Insurance

The civil liability of the involved parties with respect to financial loss due to personal injury and other damage that may arise as a result of this study being conducted are governed by the applicable legal requirement(s).

Insmed will provide insurance to the Investigator if required by the applicable regulatory and legal requirement(s).

If required by local law, participants taking part in this study will be insured against any injury caused by the study in accordance with the applicable regulatory and legal requirement(s).

10.1.16. Publication Policy

Any formal presentation or publication of data collected from this study will be considered as a joint publication by the Investigator(s) and the appropriate personnel of Insmed. Authorship will be determined by mutual agreement. For multi-center studies, it is mandatory that the first publication be based on data from all centers, analyzed as stipulated in the protocol by Insmed and statisticians, and not by the Investigators themselves. Investigators participating in multi center studies agree not to present data gathered from a single center or a small group of centers before the full, initial publication, unless formally agreed to by all other Investigators and Insmed.

Insmed must receive copies of any intended communication in advance of publication (at least 15 working days for an abstract or oral presentation and 45 working days for a journal

submission). Insmed will review the communications for accuracy (thus avoiding potential discrepancies with submissions to regulatory authorities), verify that confidential information is not being inadvertently divulged, and to provide any relevant supplementary information. Authorship of communications arising from pooled data may include members from each of the contributing centers as well as Insmed personnel.

At the conclusion of the study, after the data are analyzed, the results of study will be reported in a clinical study report.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 7 will be performed by the local laboratory. If local laboratory results are used to make a study IMP decision or response evaluation, the results must be recorded. Protocol-specific clinical laboratory requirements for the inclusion or exclusion of participants are detailed in Section 5.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 7: Protocol-Required Safety Laboratory Tests, INS1009-201

Category	Laboratory Parameters
Clinical Chemistry	Sodium, chloride, potassium, CO_2, magnesium, calcium, glucose, phosphate, total bilirubin (with direct and indirect fractionation, if total bilirubin is elevated >2 ULN), alkaline phosphatase, LDH, AST, ALT, CPK, albumin, total protein, creatinine, urea-nitrogen, uric acid, estimated glomerular filtration rate
Hematology	Hemoglobin, erythrocytes, hematocrit, MCH, MCV, MCHC, leukocytes, differential blood count of neutrophils, eosinophils, basophils, monocytes, lymphocytes, and platelets
Coagulation[a]	PT, PTT, INR
Serology[a]	HIV antibody, hepatitis B surface antigen [HBsAg], Hepatitis C virus antibody
Pregnancy test	Highly sensitive serum or urine hCG

[a] Not included in EUT screening for participants enrolling in the extended use treatment period.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; CO_2 = carbon dioxide; CPK = creatine phosphokinase; hCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; INR = international normalized ratio; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PT = prothrombin time; PTT = partial thromboplastin time; ULN = upper limit of normal

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

The definitions and procedures in this Appendix (Appendix 3) are for AEs and SAEs that do not involve the Plastiape capsule based Dry Powder Inhaler. For reporting device deficiencies or AEs involving the Plastiape capsule based Dry Powder Inhaler, please see Section 10.6.

10.3.1. Definition of AE

AE Definition
An AE is defined as any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, October 1994). A treatment emergent adverse event (TEAE) is defined as any AE that occurs after the first dose of study IMP and within 28 days after the last dose of study IMP

Events Meeting the AE Definition
Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), that worsen from Baseline, are considered clinically significant in the medical and scientific judgment of the Investigator (e.g., not related to progression of underlying disease), that are associated with signs and/or symptoms, require therapeutic intervention, or lead to discontinuation of the administration of study IMP must be reported as an AE Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. New conditions detected or diagnosed after study IMP administration even though it may have been present before the start of the study. Signs, symptoms, or the clinical sequelae of a suspected IMP- IMP interaction. Signs, symptoms, or the clinical sequelae of a suspected overdose of either study IMP or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses must be reported regardless of sequelae. The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. “Lack of efficacy” or “failure of expected pharmacological action” also constitutes an AE or SAE. Lack of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the PK and PD assessments.

Events <u>NOT</u> Meeting the AE Definition

Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.
Study INS1009-201 requires an overnight inpatient treatment period (Study Days 1-2). Complications that occur during the inpatient treatment period are AEs. If a complication prolongs the planned hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE must be considered serious.
Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.
This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is a suspected transmission of any infectious agent via an authorized medicinal product

g. Is an important medical event

h. Other situations:

Medical or scientific judgment must be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events must usually be considered serious.

g. Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of IMP dependency or IMP abuse.

10.3.3. Recording and Follow-up of AE and/or SAE

AE and SAE Recording

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The Investigator will then record all relevant AE/SAE information.

It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to Insmed in lieu of completion of the completed AE reporting form.

There may be instances when copies of medical records for certain cases are requested by Insmed. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Insmed.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities.

Severe: An event that prevents normal everyday activities. An AE that is assessed as severe must not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

The Investigator is obligated to assess the relationship between study IMP and each occurrence of each AE/SAE.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study IMP administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to Insmed. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Insmed.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Insmed to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide Insmed with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to Insmed within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

All SAEs, regardless of causality, must be reported to the organization delegated by Insmed on a Serious Adverse Event Report Form within 24 hours of becoming aware of the event; corrections and additions are required to be submitted within 24 hours. Study-specific email, phone, and fax number for SAE reporting information will be provided to the study sites.

Unexpected drug related SAEs as assessed by Insmed or authorized person qualify for expedited reporting and will be reported to the IRB, regulatory authorities, participating Investigators and, if cross reporting is required for SUSARs, in accordance with all applicable global laws and regulations. A SUSAR is a Serious Adverse Reaction, which is suspected to be caused by the investigational medicinal product and which is unexpected; e.g., its nature or severity is not

consistent with the information in the relevant Reference Safety Information. SAEs, including those that do not meet requirements for expedited reporting, and all other AEs will be reported to the regulatory agencies as appropriate (e.g., for the FDA these are reported in the Investigational New Drug annual report and for the European Medicines Agency, these are reported in the Development Safety Update Report).

SAE Reporting to Insmed via an Electronic Data Collection Tool
The primary mechanism for reporting an SAE to Insmed will be the electronic data collection tool. If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours. The site will enter the SAE data into the electronic system as soon as it becomes available. After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Medical Monitor by email or telephone.

SAE Reporting to Insmed via Paper Data Collection Tool
Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to Insmed. In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting time frames.

10.4. Appendix 4: Contraceptive and Barrier Guidance

Contraceptive use by men and women of childbearing potential (WOCBP) must be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Highly effective contraception methods include true abstinence (refraining from heterosexual intercourse during the study); combined (estrogen and progestogen containing) or progestogen only hormonal contraception associated with inhibition of ovulation and supplemented with a double barrier (preferably male condom); intrauterine devices; intrauterine hormone-releasing systems; or vasectomized partner.

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

INTRODUCTION

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a participant meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with Insmed clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug-Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

DEFINITIONS

Potential Hy's Law (PHL)

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3×ULN and total bilirubin (TBL) ≥2×ULN at any point during the study irrespective of an increase in alkaline phosphatase (ALP). The elevations do not have to occur at the same time or within a specified time frame.

Hy's Law (HL)

AST or ALT ≥3× ULN and TBL ≥2×ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug. The elevations do not have to occur at the same time or within a specified time frame.

IDENTIFICATION OF POTENTIAL HY'S LAW CASES

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

1. ALT ≥ 3xULN
2. AST ≥ 3xULN
3. TBL ≥ 2xULN

The Investigator will review without delay each new laboratory report and if the identification criteria are met will:

1. Notify Insmed representative
2. Determine whether the participant meets PHL criteria (see DEFINITIONS of this Appendix) by reviewing laboratory reports from all previous visits

3. Promptly enter the laboratory data into the laboratory CRF

FOLLOW-UP

POTENTIAL HY'S LAW CRITERIA NOT MET

1. If the participant does not meet PHL criteria the Investigator will:
2. Inform Insmed representative that the participant has not met PHL criteria.
3. Perform follow-up on subsequent laboratory results according to the guidance provided in the clinical study protocol

POTENTIAL HY'S LAW CRITERIA MET

If the participant does meet PHL criteria the Investigator will:

- Notify Insmed representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or Baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician
- Complete the 3 Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

The instructions in this section must be followed for all cases where PHL criteria were met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than drug-induced liver injury caused by the IMP. The Insmed Medical Science Director and Global Safety Physician will also be involved in this review together with other participant matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

- If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE
- If the alternative explanation is not an AE, record the alternative explanation on the appropriate CRF

If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow Insmed standard processes.

If it is agreed that there is no explanation that would explain the ALT or AST and TBL elevations other than the IMP:

•Report an SAE (report term ‘Hy’s Law’) according to Insmed standard processes.

- The ‘Medically Important’ serious criterion must be used if no other serious criteria apply
- As there is no alternative explanation for the HL case, a causality assessment of ‘related’ must be assigned.

If there is an unavoidable delay, of over 3 weeks in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term ‘Potential Hy’s Law’) applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

10.6. Appendix 6 Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

The definitions and procedures detailed in this appendix are in accordance with ISO 14155.

Both the Investigator and Insmed will comply with all local reporting requirements for medical devices.

The detection and documentation procedures described in this protocol apply to all Insmed medical devices provided for use in the study. See Section 6.1.3 for the list of Insmed medical devices.

10.6.1. Definition of Medical Device AE and ADE

Medical Device AE and ADE Definition
An AE is any untoward medical occurrence in a clinical study participant, users, or other persons, temporally associated with the use of study IMP, whether or not considered related to the investigational medical device. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved. An adverse device effect (ADE) is defined as an AE related to the use of an investigational medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.6.2. Definition of Medical Device SAE, SADE and USADE

A Medical Device SAE is an any serious adverse event that:
a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in: A life-threatening illness or injury. The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death if it were more severe. A permanent impairment of a body structure or a body function. Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function. Chronic disease (MDR 2017/745).
c. Led to fetal distress, fetal death, or a congenital abnormality or birth defect

d. Is a suspected transmission of any infectious agent via a medicinal product
SADE definition
A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of an SAE. Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.
Unanticipated SADE (USADE) definition
An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is defined as a serious adverse device effect that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report (Section 2.3).

10.6.3. Definition of Device Deficiency

Device Deficiency Definition
A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and information supplied by the manufacturer.

10.6.4. Recording and Follow-up of AE and/or SAE and Device Deficiencies

AE, SAE, and Device Deficiency Recording
When an AE/SAE/device deficiency occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. The Investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the Investigator's normal clinical practice and on the appropriate form. It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to Insmed in lieu of completion of the AE/SAE/device deficiency form. There may be instances when copies of medical records for certain cases are requested by Insmed. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Insmed. The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. For device deficiencies, it is very important that the Investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency. A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE/SAE/device deficiency reported during the study and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe must not be confused with an SAE. "Severe" is a category used for rating the intensity of an event; both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, **not** when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study IMP and each occurrence of each AE/SAE/device deficiency.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship, cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study IMP administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure and/or Instructions for Use of the device in his/her assessment.
- For each AE/SAE/device deficiency, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/device deficiency and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to Insmed. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Insmed.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE/SAE/device deficiency

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Insmed to elucidate the nature and/or causality of the AE/SAE/device deficiency as fully as

possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide Insmed with a copy of any post-mortem findings including histopathology.
New or updated information will be recorded in the originally completed form.
The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.6.5. Reporting of SAEs

SAE Reporting to Insmed via an Electronic Data Collection Tool

The primary mechanism for reporting an SAE to Insmed will be the electronic data collection tool.
If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next table) to report the event within 24 hours.
The site will enter the SAE data into the electronic system as soon as it becomes available.
After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next table) or to the Medical Monitor by telephone.

SAE Reporting to Insmed via Paper Data Collection Tool

Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to Insmed.
In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE paper data collection tool sent by overnight mail or courier service.
Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE paper data collection tool within the designated reporting time frames.

10.6.6. Reporting of SADEs

SADE Reporting to Insmed

NOTE: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

Any device deficiency that is associated with an SAE must be reported to Insmed within 24 hours after the Investigator determines that the event meets the definition of a device deficiency.

Insmed will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs as required by national regulations.

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Signature Page for INS1009-201 Protocol Amendment No. 1

Approve	[redacted] 06-Oct-2021 23:02:59 GMT+0000

CLINICAL STUDY PROTOCOL

An Open-Label Study to Assess the Safety, Pharmacokinetics, and Pharmacodynamics of Treprostinil Palmitil Inhalation Powder in Participants with Pulmonary Arterial Hypertension

Protocol Number: INS1009-201

Version Number: 2.0

Amendment Number: 1

Compound: Treprostinil Palmitil Inhalation Powder (TPIP)

Study Phase: 2a

Sponsor Name: Insmed Incorporated

Legal Registered Address:
700 US Highway 202/206
Bridgewater, NJ 08807-1704
USA

Regulatory Agency Identifier Number(s)
IND: 147264

Date: 06 OCT 2021

IMPORTANT CONTACTS

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ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ALT	alanine amino transferase
AST	aspartate amino transferase
AUC	area under the concentration-time curve
$AUC_{0-\infty}$	area under the concentration-time curve from time zero to infinity
AUC_{t1-t2}	area under the plasma concentration-time curve from time zero to time of last measurable concentration
CL/F	apparent total clearance of drug from plasma after extravascular administration
C_{max}	maximum (peak) plasma concentration of the drug
CO	cardiac output
CRF	case report form
CRO	contract research organization
CT	computerized tomography
DILI	drug induced liver injury
DPI	dry powder inhalation
ECG	electrocardiogram
EDC	electronic data capture
EOS	end of study
EUT	extended use treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice

HIV	Human Immunodeficiency Virus
HL	Hy's Law
ICF	informed consent form
ICH	International Council for Harmonisation
ICU	intensive care unit
IMP	investigational medicinal product
IRB	investigational review board
IV	intravenous
MAD	multiple ascending dose
mPAP	mean pulmonary arterial pressure
MVO_2	mixed venous oxygen saturation
NOAEL	No observed adverse effect level
NT-pro-BNP	N-terminal (NT)-pro hormone brain natriuretic peptide
PAH	pulmonary arterial hypertension
PAP	pulmonary arterial pressure
PD	pharmacodynamic(s)
PH	pulmonary hypertension
PHL	potential Hy's Law
PI	principal investigator
PK	pharmacokinetic(s)
PVR	pulmonary vascular resistance
QD	Once daily
QID	four times daily
RAP	right atrial pressure

RHC	right heart catheter
RVP	right ventricular pressure
SAD	single ascending dose
SAE	serious adverse event
SARS CoV 2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
SoA	schedule of activities/assessments
SUSAR	suspected unexpected serious adverse reaction
SRC	Safety Review Committee
$t_{1/2}$	elimination half-life
TBL	total bilirubin
TAPSE	tricuspid annular plane systolic excursion
TEAE	treatment emergent adverse event
t_{max}	time to maximum (peak) plasma concentration following drug administration
TPIP	treprostinil palmitil inhalation powder
TPIS	treprostinil palmitil inhalation suspension
TRE	treprostinil
TP	treprostinil palmitil
TVR	tricuspid valve regurgitation
ULN	upper limit of normal
US	United States
VCO_2	carbon dioxide production
Vd/F	apparent volume of distribution at terminal phase

WHO	World Health Organization
WOCBP	woman of child-bearing potential

1. PROTOCOL SUMMARY

1.1. Protocol Amendment Summary of Changes

Amendment 1 (06 OCT 2021)

This amendment is considered to be substantial.

Overall Rationale for the Amendment:

The primary driver for the changes in the protocol amendment is to provide extended access of investigational medicinal product (IMP) to the study participants.

Grammatical and typographical errors were corrected throughout the document.

A summary of major changes in this amendment, compared to the original protocol, is shown in the table below.

Revision	Rationale	Location of Revision
Updated overall design description	To include and clarify the parameters of the optional extended use treatment (EUT) period; to add reference to a separate open-label extension study	• Section 1.2 • Section 2.1 • Section 4.1 • Section 4.1.4 • Section 4.1.5 • Section 5.1
Updated the study schema	To include and clarify the parameters of the optional EUT period	• Section 1.3.1.3 • Figure 1 • Section 1.3.1.4 • Section 1.3.1.5 • Figure 3 • Section 2.3.2 • Section 2.3.3
Updated the Schedule of Activities	To include the optional EUT period and optional CT scans; to remove pharmacokinetic draw at 36 hours	• Section 1.3.1.3 • Section 1.4 • Section 4.1 • Section 4.1.2 • Section 7.1.2 • Section 8.1.5.2 • Section 8.4

Revision	Rationale	Location of Revision
Updated the definition of study completion	To add the optional EUT period to the definition of study completion	• Section 4.4
Addition of exploratory objectives	To add corresponding exploratory objectives for the EUT period	• Section 3.1
Updated Inclusion Criterion #4	To include participants with Functional Class I	• Section 5.1
Updated Inclusion Criterion #3	To remove maximum length of time for pulmonary arterial hypertension (PAH) diagnosis	• Section 5.1
Added Inclusion Criterion #18	To exclude participants receiving potent CYP2C8 inhibitors	• Section 5.2
Updated study title	Updated title of study to remove single-dose qualifier	• Title • Section 1.2
Updated cardiovascular and adverse events of special interest	To remove unexpected or common events	• Section 8.3.6
Updated PAH definition	To change mean pulmonary arterial pressure to > 20 mmHg in Inclusion Criterion #2, Inclusion Criterion #9, and generally across the document per updated guidelines	• Section 5.1 • Section 0
Updated dose selection justification	To add a subsection for the optional EUT period; to update original dose justification with additional data from Study INS1009-102	• Section 1.3.2.2 • Section 4.3.1 • Section 4.3.2
Added additional information regarding study IMP administered	To add an additional section describing the study IMP that participants entering the optional EUT period would receive	• Section 6.1.2

Revision	Rationale	Location of Revision
Clarified screening/rescreening activities	To verify participants enrolling in the optional EUT period after the initial follow-up visit still meet inclusion/exclusion criteria	• Section 1.3.1.4 • Section 1.4 • Section 4.1.1 • Section 4.1.4 • Section 5.1 • Section 5.2 • Section 6.8 • Section 8 • Section 8.2.2.2 • Section 8.2.5
Updated the description of adverse event (AE) and serious adverse event (SAE) collection	To add reference to AE and SAE collection for participants and clarify follow-up procedures	• Section 7.2 • Section 8.3 • Section 8.3.1 • Section 8.3.3
Updated information from newly completed study	To update background and safety information from Study INS1009-102	• Section 2.2 • Section 2.3.1
Updated number of study centers	To update to the most current estimation of study centers expected	• Section 5
Updated information regarding IMP preparation, handling, storage, and accountability	To include information from the EUT period and use of updated dose	• Section 6.2 • Section 6.2.2
Updated study intervention compliance description	To include and clarify details for the EUT period	• Section 6.4.2

Document History		
Document	**Version**	**Date**
Global Amendment 1	2.0	06 OCT 2021
Original Protocol	1.0	02 NOV 2020

1.2. Synopsis

Protocol Title:

An Open-Label Study to Assess the Safety, Pharmacokinetics, and Pharmacodynamics of Treprostinil Palmitil Inhalation Powder in Participants with Pulmonary Arterial Hypertension

Rationale:

Treprostinil palmitil (TP) is an inactive prodrug of treprostinil (TRE), which is widely used in the treatment of pulmonary hypertension (PH). Treprostinil palmitil inhalation powder (TPIP) is a dry powder for inhalation formulation of TP. TPIP is being developed for the treatment of pulmonary arterial hypertension (PAH; World Health Organization (WHO) Group 1 PH). TPIP is expected to provide extended release of TRE in the lung with the goals of less frequent and more convenient and consistent dosing while reducing the frequency and severity of dose-limiting side effects associated with the currently approved forms of TRE. No studies of TP or TPIP have been conducted in participants with PAH. The purpose of this study is to evaluate the safety, pharmacokinetics (PK), and pharmacodynamic (PD) effects of a single dose of TPIP in participants with PAH.

The starting and planned doses for this study are primarily based on the safety and tolerability of treprostinil palmitil inhalation suspension (TPIS) in healthy participants following single inhalation at 85 to 340 µg (Study INS1009-101) and TPIP in healthy participants in a SAD/MAD study (Study INS1009-102). In INS1009-101, the systemic exposure for TRE at 340 µg was low (AUC < 2.5 ng*h/mL) with an elimination $t_{1/2}$ of approximately 7 hours. In rats, the PK profile of TP inhalation solution was similar to that of TP inhalation powder. In INS1009-102, single doses of up to 675 µg and multiple doses of up to 225 µg for 7 days were administered to healthy participants. Overall, TP was well tolerated, with largely mild TEAEs and an adverse effect profile consistent with that of inhaled prostacyclin analogs. Treprostinil exposures increased approximately dose-proportionately, were similar between TPIS and TPIP, and showed no accumulation with once daily (QD) dosing.

Objectives and Endpoints:

Objectives	Endpoints
Primary	Primary
• To evaluate the safety and tolerability of single doses of TPIP in participants with PAH	• Frequency of TEAEs
Secondary	Secondary
• To evaluate the PD effects of single doses of TPIP on PVR in participants with PAH over the	• Change from Baseline in PVR at 8 and 24 hours after TPIP administration

first 24 hours following administration	
• To evaluate the PK of TPIP as TRE in participants with PAH	• C_{max}, t_{max}, $AUC_{t1–t2}$, $AUC_{0–\infty}$, $t_{1/2}$ of TRE in plasma

TPIP=treprostinil palmitil inhalation powder; PAH=pulmonary arterial hypertension; TEAE=treatment emergent adverse event; PD=pharmacodynamic; PVR=pulmonary vascular resistance; PK=pharmacokinetics; TP=treprostinil palmitil; TRE=treprostinil; C_{max}=maximum observed concentration; t_{max}=time to maximum concentration after drug administration; $AUC_{t1–t2}$= area under the concentration time curve from time zero to last sampling time point with measurable concentration; $AUC_{0–\infty}$=area under the concentration time curve from time zero to infinity; $t_{1/2}$=elimination half-life

Overall Design:

This is a Phase 2a open-label study to assess the safety, tolerability, PD effects, and PK of TPIP administered to participants with PAH. This is the first study of TPIP in participants with PAH. Each participant will receive a single dose of TPIP, which may vary from participant to participant, as determined by the Safety Review Committee (SRC) for the study. The study includes a 24-hour inpatient observation period following TPIP dosing, during which PK, PD, and safety parameters will be assessed. An optional extended treatment period of 16 weeks will be available to participants who have completed the single-dose inpatient treatment period. When available, participants may be eligible to enroll in a separate open-label extension study (OLE) study that will have a duration of approximately 2 years. Details of the planned OLE study will be provided in a separate protocol. The study is designed to ensure the safety of and maintain minimal risk to participants. The cardiopulmonary and overall functional status of participants with PAH can be labile and medical instability can develop quickly. As such, there is considerable flexibility built into the protocol to allow Investigator discretion with the frequency, timing, and/or conduct of PD and PK assessments to again ensure participants' safety.

Brief Summary:

The study is designed to investigate the safety and acute pharmacokinetic (PK) and pharmacodynamic (PD) effects of a single dose of treprostinil palmitil inhalation powder (TPIP) in participants with pulmonary arterial hypertension (PAH). Intensive monitoring of pulmonary vascular resistance, cardiac output, right ventricular pressure, pulmonary arterial pressure, hemoglobin, right atrial pressure, and mixed venous oxygen saturation via right heart catheter in an appropriate inpatient setting is essential to understand how TPIP affects cardiopulmonary hemodynamics and to elucidate dose- and PK-effect relationships. Some assessments and study activities (resting respiratory gas exchange assessment, transthoracic echocardiogram, pulmonary computerized tomography scan) for exploratory endpoints are optionally left to the discretion of the individual Investigator, based on participant safety and study site capabilities.

For individual participants, the study will consist of an outpatient screening period lasting up to 30 days. The inpatient treatment period will start on Study Day 1 and is expected to last

overnight into Study Day 2. Outpatient PK sampling and safety follow-up at 48 hours post TPIP dose will extend into Study Day 3. A remote safety follow-up visit (telephone visit) is scheduled for Study Day 30 (± 2 days). An optional extended treatment period of 16 weeks will be available to participants who have completed the single-dose inpatient treatment period. There will be a second safety follow-up visit 30 days (± 3 days) after extended use treatment (EUT) Week 16 for participants who elect to enter the extended use treatment period. If the initial remote safety follow-up visit overlaps with the start of the extended treatment period, the initial remote safety visit will be shortened and conducted just prior to administration of IMP in the extended treatment period.

Number of Participants:

Approximately 6 to 10 evaluable participants are planned. Evaluable participants for safety are those who receive a single dose of TPIP; evaluable participants for PD and PK endpoints are those who receive a single dose of TPIP and have at least 1 post-TPIP administration PK or PD datapoint.

Treatment Groups and Duration:
This is an open-label, non-randomized study. There are no predefined treatment groups. The dose determination for each participant will be made based on all available PK, PD, and safety data at the time of the participant's entry into the study. An optional extended use treatment period of 16 weeks will be available to all participants.

Safety Review Committee:
A Safety Review Committee (SRC) will be responsible for monitoring safety data. The SRC will comprise all Investigators and key members of the Insmed Study Team (including but not limited to Medical Monitor, Medical Director(s), Safety/Pharmacovigilance Physician, Statistician, Clinical Pharmacologist) and external expert consultants. The SRC will continuously monitor all available safety, PD and PK data for each participant and will obtain consensus regarding the safety of continuing the study, the next TPIP dose, and clinical care of the next participant. Expert consultants may be invited to review and interpret participant data. With any safety findings, a decision will be made, based on the review, as to whether enrollment in the study will be allowed to continue. Decisions regarding final database values for PD parameters may be adjudicated by the SRC.

1.3. Schema

1.3.1. Participant Progression Through the Study

The main study comprises an outpatient screening period, an inpatient treatment period, and an outpatient follow-up period. Participant progression through the study is shown in Figure 1. An optional EUT period is shown in Figure 2.

1.3.1.1. Screening Period

The outpatient screening period will last up to 30 days. After participants complete screening and have met the study eligibility criteria, the right heart catheter (RHC) procedure and inpatient treatment period should be scheduled without delay.

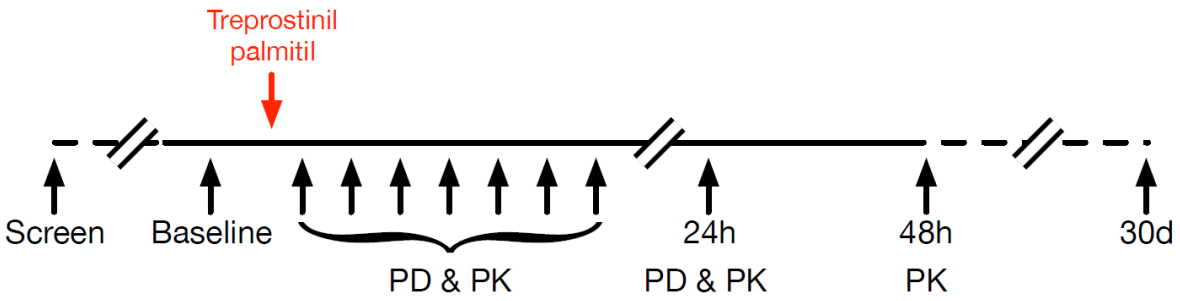
1.3.1.2. Inpatient Treatment Period

The inpatient treatment period will start on Study Day 1 and extend overnight into Study Day 2. Because the study requires an inpatient treatment period, institutional requirements for elective inpatient admissions, which may vary from site to site, will be followed. The participant may be required to undergo pre-admission assessments required by the institution for elective admission, for example testing for common infectious pathogens. Signature of elective admission documents and other consents may be required by the institution. An RHC will be placed. Following completion of Baseline assessments, a single dose of TPIP will be administered via a dry powder inhaler. Safety, PD, and PK assessments will continue at scheduled intervals through 24 hours following TPIP administration. Following the final assessments at 24 hours, the RHC will be removed and the participant will be discharged from the inpatient setting when deemed safe for the participant.

1.3.1.3. Follow-up Period

PK blood draw at 48 (± 4) hours after TPIP dosing will be done on an outpatient basis as arranged by the site. The 48-hour post-TPIP visit will also include safety assessments including physical examination, clinical laboratory evaluations, ECG, AE collection and vital signs. An additional safety follow-up will be conducted by telephone call or telemedicine on Study Day 30 (± 2 days) unless the participant elects to enter the EUT period prior to this follow-up visit. If the initial remote safety follow-up visit overlaps with the start of the extended treatment period, the initial remote safety visit will be shortened and conducted just prior to administration of investigational medicinal product (IMP) in the extended treatment period.

Figure 1: Participant Progression Through INS1009-201 Study[a]



PD-pharmacodynamic assessments; PK=pharmacokinetic assessments; h=hours; d=days

[a] Does not include optional extended use treatment period; the 30 day follow-up visit will be shortened and conducted just prior to administration of IMP in the extended treatment period if the visit overlaps with the start of the extended treatment period.

1.3.1.4. Optional Extended Use Treatment Period

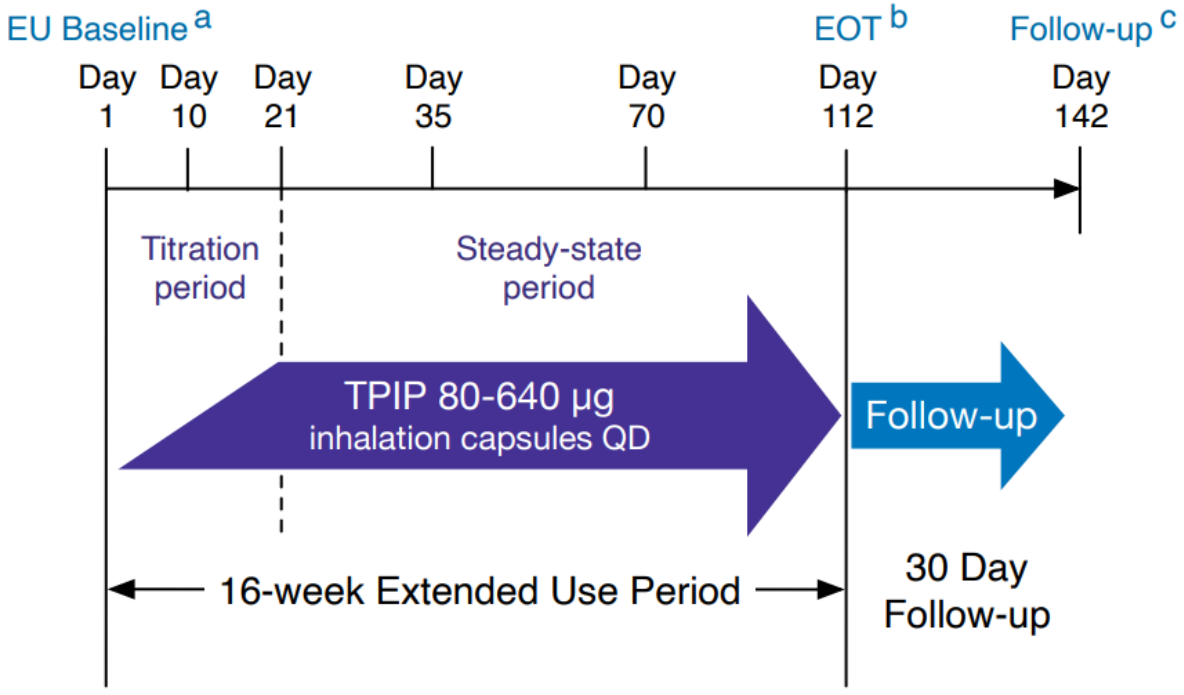
All participants will be allowed to enter the optional 16 week EUT period after the completion of the inpatient treatment period and final PK sample collection. Entry into the optional EUT period will be at participant and Investigator discretion. A gap between the inpatient treatment period and EUT period is expected, but not required, and can be up to 6 months.

After collection of the final PK sample, all participants will be allowed optional continued access to IMP for 16 weeks (includes a 3-week titration period) from first administration in the EUT period. At the Investigator's discretion, participants may undergo a study drug taper for up to 2 weeks after the Week 16 visit to help facilitate a safe withdrawal from study drug.

Participants will be screened to ensure they meet inclusion and exclusion criteria if they enter the EUT period more than 30 days after beginning the single-dose period (e.g., beyond the initial 30 day follow-up period) (Table 5).

Participant in-clinic study visits will be scheduled for EUT at Baseline (EUT Day 1), EUT Week 2, EUT Week 3, EUT Week 5, EUT Week 10, and EUT Week 16.

Figure 2: Participant Progression Through the Optional Extended Use Treatment Period



[a] The 30 day follow-up visit from the single dose period will occur on EU Day 1 if the visit overlaps with the start of the extended treatment period.
[b] At the Investigator's discretion, participants may undergo a study drug taper for up to 2 weeks after the Week 16 visit.
[c] The follow-up telephone call or visit will be 30 days after the Week 16 visit.
EU = Extended Use; QD = once daily; EOT = end of treatment

1.3.1.5. Extended Use Follow-up Period

There will be a second remote safety follow-up visit 30 days (± 3 days) after EUT Week 16 administration for participants who elect to enter the EUT period.

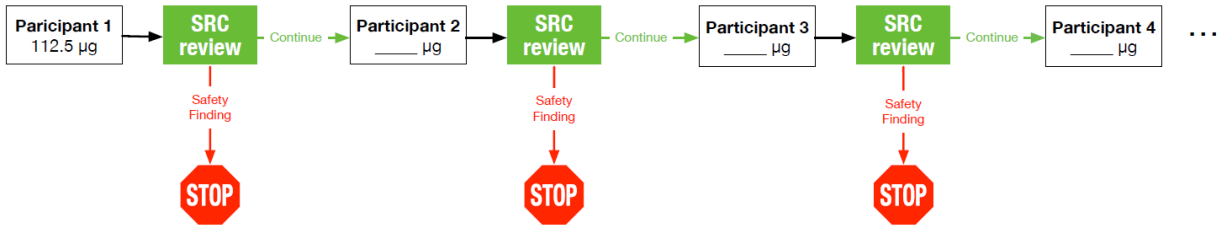
1.3.2. Dose Selection

1.3.2.1. Inpatient Treatment Period Dose Selection

Each participant will enter the study in a serial fashion, following review of available safety, PK, and PD data from all previous participants by the Safety Review Committee (SRC). Each participant will receive a single-dose administration of TPIP via a dry powder inhaler. TPIP will be administered to only one participant at a time, with full evaluation of all available data prior to dosing the next participant.

The first participant will receive a dose of TPIP containing 112.5 µg of TP. The SRC will then review all available safety, PD, and PK data including data from the first participant and select the TPIP dose and any changes to the assessments for the second participant. Then, following review of all available data including that from the first and second participants, the SRC will select the dose for the third participant. Similarly, all available data from previous studies and participants will be assessed prior to determining the dose for the next participant, until such a time as the SRC believes the study must conclude. Figure 3 describes the planned dose-selection and study continuation process.

Figure 3: Schematic of Study Continuation Planning after Participant 1, INS1009-201



SRC=Safety Review Committee

1.3.2.2. Optional Extended Use Treatment Period

Entrance into the optional EUT period is at participants' and Investigators' discretion and begins with a titration. The guideline for the optimal 3-week planned titration schedule is provided in Figure 4. The target TPIP dose will be achieved with a combination of dry powder capsules containing 80 µg, 160 µg, and 320 µg of TP.

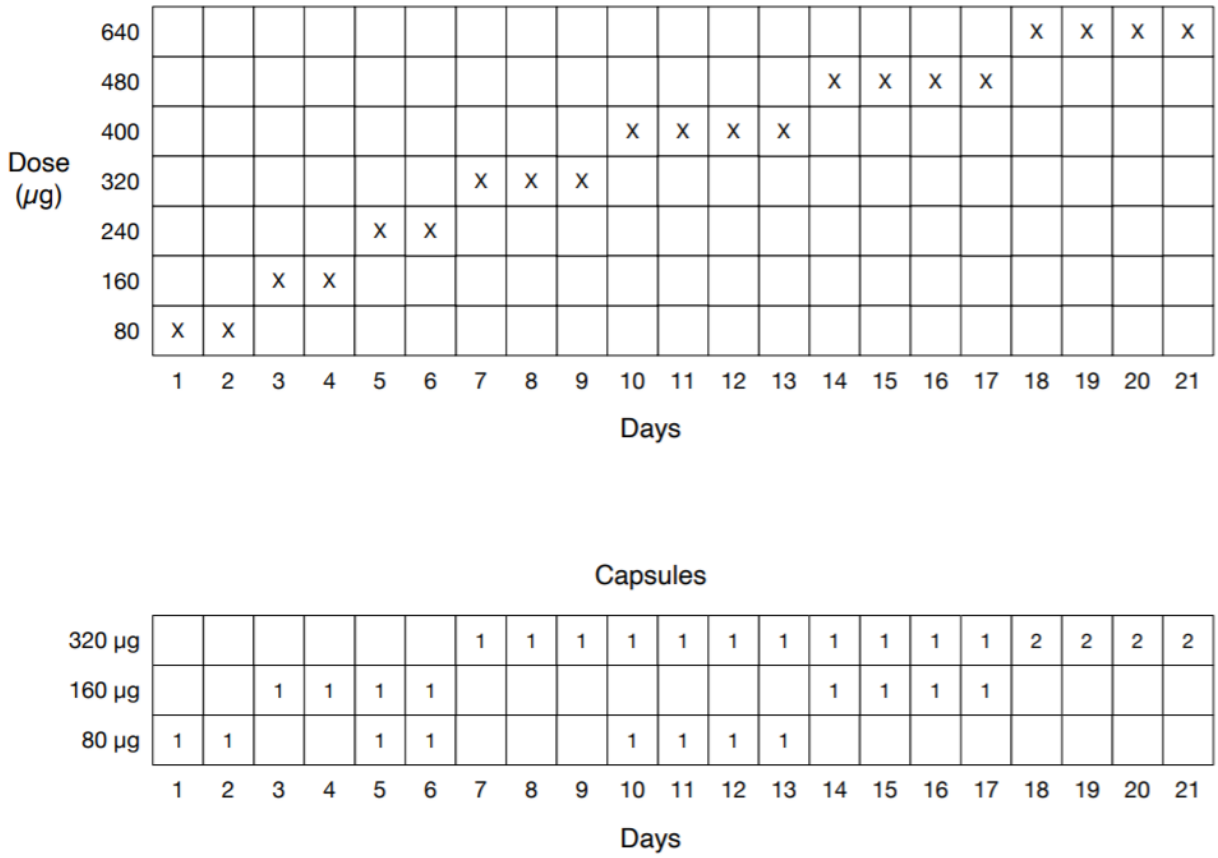
During the titration period (EUT Days 1 to 21), each participant's dose will be up-titrated to the highest tolerated dose for that individual. Participants will start open-label study drug with 1 capsule (80 µg TPIP) QD. If this dose is well tolerated, the dose should be up-titrated until reaching the participant's highest tolerable dose as described by the dosing schedule in Figure 4. During this titration period, participants must stay on study drug for the minimum number of cumulative days required for each dose (e.g, 2 days at 80 µg, 160 µg, or 240 µg; 3 days at 320 µg; or 4 days at 400 µg or 480 µg) prior to titrating to the next higher dose. Study drug titration may occur slower, but not faster, than described in Figure 4. If a dose is not tolerated, study drug may be decreased to the previous dose level. At the Investigator's discretion, up-titration may resume (as described in Figure 4) until the participant's highest tolerated dose is achieved at EUT Day 21.

All dose adjustments must be preceded by contact with the Investigator or study site personnel. In addition, the Investigator and/or study site personnel will be in contact with participants during the dose adjustment period to assess the tolerability to study drug as measured by the AEs commonly observed with other prostacyclin receptor agonists, which include headache, flushing, nausea, cough, and muscle pain. The decision to up-titrate to the next TPIP dose will be based on safety and tolerance data (e.g., AEs) as reported by the participant and assessed by the Investigator.

At the Investigator's discretion, based on tolerability, the study drug dose may be increased by 1 dose level (as described in Figure 4) at the EUT Week 5 in-clinic visit for participants who have not achieved the 640 µg dose. The increase in dose will be administered under clinical observation at the study site to ensure tolerability and correct dosing and self-administration of study drug. The participant's highest dose tolerated is expected to continue for the remainder of the study after the EUT Week 5 visit.

At the Investigator's discretion, participants may undergo a study drug taper for up to 2 weeks after the EUT Week 16 visit to help facilitate a safe withdrawal from study drug. The Investigator and/or study site personnel will be in contact with participants during the study drug taper to assess the tolerability to study drug.

Figure 4: Guideline for Optimal 3-Week Planned Titration Schedule (Optional Extended Use Treatment Period)



1.4. Schedule of Activities (SoA)

The SoA is divided into the following tables:

- Screening and follow-up activities in the single-dose period
- SoA in the inpatient treatment period
- PK and PD biomarker blood sampling schedule
- Optional procedures and assessments in the inpatient treatment period
- Screening and follow-up activities in the EUT period
- SoA in the EUT period

The single-dose period refers to the combination of the inpatient treatment period (Study Day 1 to Study Day 2), the PK/PD sampling period, and the 30 day follow-up period.

Table 1: Schedule of Activities for Screening and Follow up, Single-Dose Period, INS1009-201

Procedure	Screening	Follow-up	
	Up to 30 Days	48 h post TPIP dose[a]	Study Day 30 (± 2 days)[b]
Informed Consent	X	--	--
Inclusion/Exclusion Criteria	X	--	--
Demographics and Medical History	X	--	--
Smoking Status	X	--	--
Height, Weight, BMI Calculation	X	--	--
Prior/Concomitant Medications	X	X	X
Serology (HBsAg, HIV antibody, HCV antibody)	X	--	--
Serum Pregnancy Test (WOCBP only)	X	—	—
Urine Pregnancy Test (WOCBP only)	--	—	X
Hematology, Clinical Chemistry (Table 7)	X	X	--
Coagulation Profile (Table 7)	X	--	--
NT-pro-BNP Sample (if needed, Section 5.1)	X	--	--
12-lead ECG	X	X	--
Physical Examination	X	X	--
Vital Signs	X	X	--
6 Minute Walking Distance Test (if needed, Section 5.1)	X	--	--
Pulmonary Function Testing (if needed, (Section 5.1)	X	--	--
Adverse Events[c]	X	X	X

[a] 48 h safety follow-up assessments are to be conducted at the time of the visit for the 48h PK blood draw (Table 3).
[b] Follow-up visit will be shortened and conducted just prior to administration of IMP in the extended treatment period if the visit overlaps with the start of the extended treatment period.
[c] AE collection is from the time of signing the informed consent through the Day 30 safety follow-up. Events between ICF signing and TPIP dosing that are serious will be recorded as SAE; non-serious events during this period must be recorded as medical history.
Note: Additional safety follow-ups may be conducted at any time per the investigator's discretion to ensure participant safety. The reason for any additional safety follow-up must be reported as an AE.
BMI = body mass index; ECG = electrocardiogram WOCBP = woman of childbearing potential

Table 2: Schedule of Activities for Inpatient Treatment Period, INS1009-201

Treatment Period (Study Day 1 to Study Day 2)											
	Pre-TPIP Administration	**TPIP Administration**	**Post-TPIP Administration**								
Procedure	Day 1 Baseline	Time 0	30 min	60 min	90 min	2 h	3 h	4 h	8 h	24 h	24 h to discharge
Hematology, clinical chemistry, coagulation profile blood draw[a]	X	--	--	--	--	--	--	--	--	X	--
Urine pregnancy test (WOCBP only)	X	--	--	--	--	--	--	--	--	--	--
12-lead ECG	X	--	--	--	--	--	--	--	--	--	--
Cardiac telemetry per institutional protocol[b]	X	←	—	—	—	—	—	—	—	—	→
Physical Exam	X	--	--	--	--	--	--	--	--	--	X
Vital signs[c]	X		X	X	X	X	X	X	X	X	X
Concomitant medications	X	←	—	—	—	—	—	—	—	—	→
Adverse events collection	X	←	—	—	—	—	—	—	—	—	→
Place right heart catheter	X	--	--	--	--	--	--	--	--	--	--
PD assessments: PVR, MVO_2, Hgb, RVP, PAP CO, PVR, RAP, oxygen consumption, PCWP (Baseline only)[d], heart rate, SpO_2, systemic blood pressure[e]	X	--	X	X	X	X	X	--	X	X	--

Treatment Period (Study Day 1 to Study Day 2)											
	Pre-TPIP Administration	**TPIP Administration**	**Post-TPIP Administration**								
Procedure	Day 1 Baseline	Time 0	30 min	60 min	90 min	2 h	3 h	4 h	8 h	24 h	24 h to discharge
Administer TPIP	--	X	--	--	--	--	--	--	--	--	--
Remove RHC	--	--	--	--	--	--	--	--	--	--	X
Discharge/Safety Follow-up Instructions	--	--	--	--	--	--	--	--	--	--	X

[a] See Section 10.2, Table 7 for specific laboratory tests.

[b] Routine cardiac telemetry readings will not be collected as study data unless they pertain to a relevant adverse event.

[c] Heart rate, systemic blood pressure, and SpO_2 are required PD measurements and will be collected as scheduled. They may be measured with pulse oximetry for heart rate and SpO_2 and an automated inflatable arm cuff for blood pressure. Temperature and respiratory rate may be measured per institutional inpatient protocol. Respiratory rate will be measured as part of pulmonary gas exchange testing, if performed.

[d] PCWP is measured at Baseline only to ensure study eligibility (Section 5.1).

[e] Systemic blood pressure must include 3 values: systolic, diastolic, and mean arterial pressure.

CO = cardiac output; Hgb = hemoglobin; MVO_2 = mixed venous oxygen saturation; PAP = pulmonary arterial pressure; PVR=pulmonary vascular resistance; RAP = right atrial pressure; RVP = right ventricular pressure; SpO_2 = arterial blood oxygen saturation; WOCBP = woman of childbearing potential

Table 3: PK and PD Biomarker Sampling Schedule, Single-Dose Period, INS1009-201

--	**Baseline Pre-TPIP Administration**	**TPIP administration**	**Post-TPIP Administration**						
Time	--	0	30 (± 10) mins	60 (± 10) mins	2 h (± 20) mins	4 (± 1) h	8 (± 2) h	24 (± 2) h	48 (± 4) h
PK sampling[a]	X	--	X	X	X	X	X	X	X
Biomarker sampling[b]	X	--	--	--	--	X	X	--	--

[a] PK sampling for treprostinil palmitil and treprostinil; each PK sample will be approximately 10 mL.

[b] Each biomarker sample will be approximately 5 to 7 mL.

Table 4: Schedule for Optional Procedures and Assessments, Inpatient Treatment Period, INS1009-201

Inpatient Treatment Period (Study Day 1 to Study Day 2)										
	Pre-TPIP Administration	**TPIP Administration**	**Post-TPIP Administration**							
Procedure	Study Day 1 Baseline	Time 0	2-8 hr	4-8 hr						
Transthoracic echocardiogram (LVEF,TVR maximum velocity, TAPSE, end diastolic right ventricular volume)	X	--	X	--						
Pulmonary CT scan (total blood volume, blood volume in vessels < 5 mm^2)	X	--	--	X						
--	**Pre-TPIP Administration**	**TPIP Administration**	--							
--	Study Day 1 Baseline	Time 0	30 mins	60 mins	90 mins	2 h	3 h	4 h	8 h	24 h
Resting respiratory gas exchange assessment[a] (respiratory rate, minute ventilation, VCO_2, ETO_2, $ETCO_2$, SpO_2	X	--	X	X	X	X	X	--	X	X

[a] Resting respiratory gas assessment parameters are collected at the same time points as RHC parameters.

NOTE: Parameters to be measured for each procedure are in parentheses.

CT=computerized tomography; $ETCO_2$ =end tidal carbon dioxide concentration; ETO_2,=end tidal oxygen concentration; LVEF=left ventricular ejection fraction; SpO_2=arterial blood oxygen saturation; TAPSE=tricuspid annular plane systolic excursion; TVR=tricuspid valve regurgitation; VCO_2,=carbon dioxide production

Table 5: Schedule of Activities for Screening and Follow-up, Extended Use Treatment Period, INS1009-201

Procedure	Screening[a]	Follow-up
	EUT Study Day 1 (± 3 days)	EUT Study Day 142 (± 3 days)
Informed Consent	X	--
Inclusion/Exclusion Criteria	X	--
Demographics	X	--
Smoking Status	X	--
Height, Weight, BMI Calculation	X	--
Prior/Concomitant Medications	X	X
Urine Pregnancy Test (WOCBP only)	X	X
Hematology, Clinical Chemistry (Table 7)	X	--
NT-pro-BNP Sample (if needed, Section 5.1)	X	--
Vital Signs	X	--
6 Minute Walking Distance Test (if needed, Section 5.1)	X	--
Adverse Events[b]	X	X

[a] Participants will only be screened at EUT Day 1 if they enter the EUT period beyond 30 days after beginning the single-dose period (e.g., beyond the initial 30 day follow-up period).
[b] AEs for the period from the Study Day 30 follow-up until the enrollment in the EUT period will be collected during participants' screening for the EUT.
BMI = Body Mass Index; EUT = extended use treatment; WOCBP = woman of childbearing potential

Table 6: Schedule of Activities for the Optional Extended Use Treatment Period, INS1009-201

Period	Extended Use Treatment Period						Follow-Up	E/D[a]
Week	EUT W1	EUT W2	EUT W3	EUT W5	EUT W10	EUT W16	EUT W20[b]	
Day	EUT D1 (Screening[c] and Baseline)	EUT D10 (± 3 days)	EUT D21 (± 3 days)	EUT D35[d] (± 3 days)	EUT D70 (± 3 days)	EUT D112 (± 3 days)	EUT D142 (± 3 days)	
Visit	EUT V1	EUT V2	EUT V3	EUT V4	EUT V5	EUT V6	EUT V7	
Prior/concomitant medications	→	→	→	→	→	→	→	→
Pregnancy test (WOCBP only)[e]	X	→	→	→	→	→	→	X
Vital signs[f]	X	X	X	X	X	X		X
6MWD test	X					X		
Hematology, clinical chemistry[c] [g]	X[c]							
NT-pro-BNP Sample[c]	X[c]					X[c]		
Optional pulmonary CT scan (total blood volume, blood volume in vessels < 5 mm^2)	X					X		
Study drug distribution[h]	X	X	X	X	X	X		
Study drug self-administration re-assessment[i]		X	X	X	X	X		
Participant diary	→	→	→	→	→	→		
Adverse events[j]	→	→	→	→	→	→	→	→

[a] Participants who enroll in the optional EUT period and discontinue before the end of study will be classified as early discontinuations.
[b] Follow-up telephone call or visit will be 30 days after the EUT Week 16 visit.
[c] Only required if first participant visit occurs after the 30 day follow-up period in the single-dose period.
[d] At the Investigator's discretion, an increase of 1 dose level may be allowed at EUT Week 5 if the participant has not achieved the 640 µg dose.

[e] Pregnancy test: Urine pregnancy tests will be performed in-clinic at EUT Baseline (EUT Day 1) in WOCBP. WOCBP will be provided home pregnancy test kits with instructions to conduct the pregnancy tests every 30 days or more if required during the treatment and follow-up periods. Study site personnel will contact the participant every 30 days by telephone and record the pregnancy test results. An additional on-site urine test must be performed prior to starting any procedure that requires the use of ionizing radiation.

[f] Vital signs: Includes body temperature (°C), pulse rate (bpm), respiratory rate (breaths/min), blood pressure (systolic, diastolic and mean arterial [mmHg]), and SpO_2. Vital signs will be measured at EUT Screening/Baseline (EUT Day 1), EUT Week 2, EUT Week 3, EUT Week 5, EUT Week 10, and EUT Week 16 and at the Early Discontinuation visit, if appropriate.

[g] See Table 7 for additional information.

[h] Participants will receive study drug supply on EUT Day 1 and at EUT Week 2, EUT Week 3, EUT Week 5, and EUT Week 10 visits. Participants who undergo a study drug taper will receive study drug supply at the EUT Week 16 visit. A telephone call from study personnel or the Investigator will be placed to participants assigned to a study drug taper to check on the participant's well-being; timing of the telephone call will be based on the Investigator's discretion, and any adverse events will be captured on the CRF.

[i] Assessment of study drug self-administration: Study drug self-administration will be overseen by study site personnel at all in-clinic visits.

[j] AE collection from the 30 day follow-up period in the single-dose period to enrollment in the EUT period will be queried during EUT screening; All other AEs and SAEs will be collected from EUT Day 1 and followed up as described in Section 8.3.3.

6MWD = 6-minute walk distance; CT = computerized tomography; CRF = case report form; D = day; E/D = early discontinuation; EUT = extended use treatment; NT-pro-BNP = N-terminal pro B-type natriuretic peptide; W = week; WOCBP = woman of childbearing potential; V = Visit

2. INTRODUCTION

Pulmonary hypertension (PH), a hemodynamic state characterized by resting mean PAP > 20 mmHg per updated guidelines (Simonneau et al., 2019), is generally classified into 5 groups based on the underlying pathology: Group 1 is PH due to pulmonary vascular disease, also known as pulmonary arterial hypertension (PAH); Group 2 is PH due to left heart disease; Group 3 is PH due to lung disease or hypoxia; Group 4 is PH due to chronic thromboembolic disease or other pulmonary vasculature obstruction; Group 5 is miscellaneous PH syndromes caused by a variety of disorders such as hemolytic anemias and sarcoidosis (Thenappan et al., 2018).

In Group 1 PH (PAH), the resting mean PAP > 20 mmHg occurs in the setting of normal pulmonary arterial wedge pressure of ≤15 mm Hg with PVR of ≥3 Wood Units (WU) (McLaughlin et al., 2009). In PAH the pulmonary vasculature is affected by vasoconstriction, vascular remodeling, increased rigidity of vessel walls and vascular fibrosis. These vascular anomalies increase PVR, which leads to increases in right ventricular afterload, and a cascade of maladaptive changes to the heart including right ventricular hypertrophy, ischemia and fibrosis, reducing right ventricular function and eventually leading to right ventricular failure and death (Thenappan et al., 2018). The pulmonary vascular lesions of PAH may be idiopathic, hereditary, or occur as a complication of drug use (e.g., anorexigens), connective tissue disease, portal hypertension, congenital cardiac malformations or HIV infection (Hoeper et al., 2017).

Data from PAH registries around the world (Thenappan et al., 2018) estimate a global incidence ranging from 2.0 to 7.6 cases per million adults per year, with a prevalence of 11 to 26 cases per million adults; the incidence in females is approximately 4 times that in males. Most registries report a mean age of onset ranging from approximately 36 to 53 years. While overall median survival has improved from 2.8 years in the 1980's to 6 years currently, mortality is high, with 1 year survival ranging from 68% to 93% and 5 year survival ranging from 21% to 65%. Nearly half of the patients in these registries have PAH of idiopathic, heritable or anorexigen-induced origin.

PAH is a debilitating progressive disease that causes a wide range of non-specific symptoms including, dyspnea, shortness of breath, chest pain, fatigue, generalized weakness and exertional syncope (Delcroix and Howard, 2015), severely affecting the patient's physical mobility, emotional and social well-being, ability to perform activities of daily living and overall quality of life. Pharmacological treatments are available to mitigate disease symptoms and slow disease progression, but treatment-related AEs, inconvenience and side effects can be treatment-limiting and negatively influence the patient's daily life (Delcroix and Howard, 2015).

The currently available pharmacologic treatments for PAH include calcium channel blockers, guanylate cyclase stimulators, endothelin receptor antagonists, phosphoesterase type 5 inhibitors, and prostanoids and prostacyclin agonists. Prostanoids, such as TRE, are among the most effective medications for the treatment of PAH. However, they are limited by the need for inconvenient and frequent drug administration and dose-limiting side effects (Thenappan et al., 2018).

2.1. Study Rationale

Treprostinil palmitil (TP) is an inactive prodrug of treprostinil (TRE). TPIP is a dry powder for inhalation formulation of TP. TPIP is being developed for the treatment of PAH. TPIP is expected to provide extended release of TRE in the lung with the goals of less frequent and more convenient and consistent dosing while reducing the frequency and severity of dose-limiting side effects associated with the currently approved forms of TRE. TP has been previously studied in healthy volunteers as an inhalation suspension (treprostinil palmitil inhalation suspension, TPIS), in single doses up to 340 µg (Study INS1009-101), and TPIP has been previously studied in a single ascending dose/multiple ascending dose (SAD/MAD) study in healthy volunteers (Study INS1009-102).

No studies of TP or TPIP have been conducted in participants with PAH. Study INS1009-201 is an open label, non-randomized, single- dose study designed to evaluate the safety, pharmacokinetics (PK), and pharmacodynamic (PD) effects of a single dose of TPIP in participants with PAH. An optional EUT period was added to maximize participant convenience and accessibility.

2.2. Background

Treprostinil is a tricyclic benzidene analogue of prostacyclin. As such, TRE has vasodilatory and anti-platelet activity within the pulmonary vascular system, thereby reducing blood flow resistance and improving the clinical state, functional class, exercise capacity, and quality of life of patients with PAH (Vachiery and Naeije, 2004).

Treprostinil has a high potency but is short-lived in the body and must be administered by continuous IV or SC infusion, or given multiple times per day by inhaled or oral routes. At present, TRE is available in the United States in formulations of IV or SC infusion (Remodulin Package Insert, 2018), oral extended-release tablets (Orenitram Package Insert, 2019), and inhalation solution (Tyvaso Package Insert, 2017) to treat PAH. The clinical experience with TRE suggests that most of the AEs experienced are related to its effects on prostanoid metabolism (e.g., headache, nausea, diarrhea, flushing, and hypotension). Dose-limiting side effects correlate to systemic plasma concentrations of TRE.

Treprostinil palmitil is a hexadecyl ester prodrug of TRE. In the lung, TP is hydrolyzed by esterase to TRE and hexadecanol. TPIP is a dry powder formulation of TP designed to provide sustained release of TRE in the lung over a prolonged period, thus providing prolonged vasodilation in the lung vasculature. This effect was demonstrated in a rat acute hypoxia model that showed a maximal reduction in PAP through the 3-hour monitoring limit with TP, while the effect of inhaled TRE started to diminish by 1 hour and was completely gone after approximately 2.5 hours. The prolonged lung exposure and pharmacological action of TRE achieved with sustained release from the prodrug TP aims to reduce both dosing frequency and side effects driven by fluctuations of plasma levels of TRE.

Treprostinil palmitil was well tolerated in rats and dogs following 16-week once-daily inhalation. At no observed adverse effect level (NOAEL) doses, the plasma C_{max} and AUC of TRE at steady

state in rats (2000 µg/kg/day) were 11 ng/mL and 73 ng*h/mL, respectively, and in dogs (250 µg/kg/day) were 1.2 ng/mL and 13 ng*h/mL, respectively.

Thus far, TP has been studied in 2 Phase 1 studies of healthy participants: An SAD study of TPIS (Study INS1009-101) and an SAD/MAD study of TPIP (Study INS1009-102). Single doses of up to 675 µg and multiple doses of up to 225 µg for 7 days were administered to healthy participants. Overall, TP was well tolerated, with largely mild treatment-emergent adverse events (TEAEs) and an adverse effect profile consistent with that of inhaled prostacyclin analogs. Treprostinil exposures increased approximately dose-proportionately, were similar between TPIS and TPIP, and showed no accumulation with QD dosing. Doses of TP achieved were several-fold higher than label-indicated target dose of inhaled treprostinil (54 µg). When comparing TPIS to inhaled treprostinil, TP had a 10-fold lower maximum plasma concentration (89.0 pg/mL vs. 958 pg/mL) and a markedly longer half-life (5.69 hours vs. 0.485 hours) than inhaled treprostinil at the molar equivalent dose. Half-life of TP was even longer with TPIP, ranging from 8.67 to 11.6 hours. These differential PK of TP may offer therapeutic advantages over treprostinil with the need for less frequent administration (QD vs QID), fewer adverse effects, and potentially improved efficacy with higher tolerated dose.

Additional information regarding the results of non-clinical and clinical studies of TP are provided in the Investigator's Brochure.

2.3. Benefit/Risk Assessment

Detailed information about the known and expected benefits and risks and reasonably expected TEAEs for TPIP from clinical and non-clinical studies may be found in the Investigator's Brochure.

2.3.1. Risk Assessment

There is no TPIP experience in participants with PAH; however, the active component, TRE, like other prostanoids and their agonists, has a well-characterized safety profile. This will help enable participants to be adequately monitored during the study.

Insmed has conducted a SAD study of TPIS in healthy volunteer participants, with safety and tolerability findings similar to those of other prostanoids (Study INS1009-101). In this study, 32 TEAEs were reported for 11 of 18 participant who received TPIS. No fatal TEAEs were reported and no TEAEs led to the withdrawal of participants. One participant who received a single dose of TPIS containing 340 µg of TP experienced several interrelated AEs that culminated in 2 TEAEs of severe and life-threatening intensity, as judged by the Investigator. The Investigator believed a severe TEAE of micturition syncope was precipitated by a TEAE of chest pain, which was assessed as probably related to the study IMP and increased vagal tone during micturition. Follow-up evaluation by an external cardiologist reveled that the participant had Tachy-Brady syndrome. A serious adverse event (SAE) of cardiac pause/nodal arrhythmia was reported for this participant and assessed as probably related to TPIS. Beyond this event, 7 TEAEs were assessed as being of moderate intensity and 23 TEAEs to be of mild intensity.

The most frequently reported TEAEs among participants receiving TPIS were cough (5 events for 5 participants), dyspnea (4 events for 4 participants), and throat irritation (4 events for

4 participants). Other TEAEs reported for more than 1 participant receiving TPIS included nausea (3 events for 3 participants) and headache (2 events for 2 participants).

There was a dose-related trend in the incidence of TEAE reporting with increasing dose levels of TPIS: 5 TEAEs were reported for 2 participants after receiving a single TPIS dose containing 85 µg of TP, 7 TEAEs were reported for 4 participants after receiving a single TPIS dose containing 170 µg of TP, and 20 TEAEs were reported for 5 participants after receiving a single TPIS dose containing 340 µg of TP.

Safety results from a recently conducted SAD/MAD study of TPIP in healthy volunteer participants (Study INS1009-102) support the TPIP dosing and management of participant safety for this study. In this study, TPIP was generally safe and well tolerated. TEAEs reported with TPIP were consistent to those seen with other inhaled prostanoid therapies. The majority of TEAEs were judged by the Investigator to be of mild intensity; there were few moderate TEAEs and no severe TEAEs across the study. No participants reported AEs of severe intensity, and no SAEs were reported. There was 1 participant in the MAD panel who discontinued after 2 doses. TEAEs were more frequent with increasing TPIP doses. In the MAD panel, participants titrated from TPIP 112.5 µg QD to 225 µg QD experienced fewer TEAEs than those who received 225 µg QD at treatment initiation, and all TEAEs were of mild severity.

Nonserious adverse events (AEs) observed in clinical studies to date are known for the pharmacological class of prostacyclin vasodilators and are considered expected for TPIP. No serious adverse reactions are considered expected for TPIP. Please refer to the Reference Safety Information in Section 6.1 of the Investigator's Brochure.

Risks inherent in study procedures and in the inpatient treatment period will be managed per Investigator and institutional processes. It is possible that the RHC-dependent Baseline parameters may indicate that the participant does not meet study inclusion criteria, may meet exclusion criteria, or is otherwise not suitable for study participation; in this case the Investigator may end the RHC procedure and not administer TPIP.

In general, an RHC is left in place for 30 to 60 minutes to take necessary measurements. This study requires the RHC to be in place for approximately 24 hours. Excess risks with prolonged placement of the RHC may include but not be limited to dislodging of the RHC, infection, bleeding, clot formation, and participant discomfort.

2.3.2. Benefit Assessment

TPIP is being developed for the treatment of PAH. TPIP may or may not result in beneficial effects for participants with PAH by providing extended release of TRE in the lung with less frequent and more convenient dosing.

2.3.3. Overall Benefit: Risk Conclusion

Although participants may or may not benefit individually from this study, risks to their well-being will be carefully monitored and managed throughout their participation. Insmed considers the risks to be appropriate to the value of the knowledge gained in this study about the characteristics of this promising therapy. The well-characterized safety profile of TRE and the

continued safety monitoring by both the Investigator and SRC (in the inpatient treatment period, observation period, and optional EUT period, if applicable) will minimize risk to participants. Most TEAEs observed with exposure to this drug are events known to be associated with prostanoids and their agonists. Study inclusion and exclusion criteria will help to ensure that only appropriate participants are enrolled. Risks involved with study procedures and settings will be managed by the relevant Investigator and institutional processes.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	**Primary**
• To evaluate the safety and tolerability of single doses of TPIP in participants with PAH	• Frequency of TEAEs
Secondary	**Secondary**
• To evaluate the effects of single doses of TPIP on PVR in participants with PAH over the first 24 hours following administration	• Change from Baseline in PVR at 8 and 24 hours after TPIP administration
• To evaluate the PK of TRE in participants with PAH	• C_{max}, t_{max}, $AUC_{t1–t2}$, $AUC_{0–\infty}$, $t_{1/2}$ of TRE in plasma
Exploratory	**Exploratory**
• To evaluate the PD effects of single doses of TPIP in participants with PAH over 24 hours following administration	• Change from Baseline in PVR, PAP, RVP, RAP, CO, oxygen consumption, MVO_2, SpO_2, heart rate, systemic blood pressure, hemoglobin, at selected time points after TPIP administration
• To evaluate the effect of single doses of TPIP on selected biomarkers in participants with PAH over 24 hours following administration	• Change from Baseline in selected biomarker concentrations at selected time points after TPIP administration
• To evaluate changes in clinical laboratory parameters in participants with PAH after TPIP administration	• Clinically relevant change from Baseline in hematology, coagulation and clinical chemistry parameters (Section 10.2, Table 7)
• To evaluate the PK of TP in participants with PAH	• Plasma PK parameters of TP, such as C_{max}, t_{max}, $AUC_{t1–t2}$, $AUC_{0–\infty}$, $t_{1/2}$, CL/F and Vd/F

• To evaluate the PK of TRE in participants with PAH	• Plasma PK parameters of TRE, such as C_{max}, t_{max}, $AUC_{t1–t2}$, $AUC_{0–\infty}$, $t_{1/2}$, CL/F and Vd/F
• To evaluate the effects of TPIP on resting respiratory gas exchange in participants with PAH[a]	• Change from Baseline in respiratory rate, minute ventilation, VCO_2, ETO_2, $ETCO_2$, SpO_2 over 24 hours after TPIP administration
• To evaluate the effects of TPIP on parameters of right ventricular function in participants with PAH as measured by transthoracic echocardiogram[b]	• Change from Baseline in LVEF, TVR maximum velocity, TAPSE, and end diastolic right ventricular volume at 2 to 8 hours after TPIP administration
• To evaluate the effects of TPIP on pulmonary vasculature and blood flow parameters in participants with PAH as measured by pulmonary CT scan[c]	• Change from Baseline in total blood volume, blood volume in vessels < $5mm^2$ at 4 to 8 hours after TPIP administration

[a] Respiratory gas exchange testing optional at Investigator discretion
[b] Echocardiogram optional at Investigator discretion
[c] Pulmonary CT scan optional at Investigator discretion
$AUC_{0–\infty}$ = area under the concentration time curve from time zero to infinity; AUC_{t1-t2} = area under the concentration time curve from time zero to last sampling time point with measurable concentration; C_{max} = maximum observed concentration after drug administration; CL/F = apparent total clearance; CO = cardiac output; CT = computerized tomography; $ETCO_2$ = end tidal carbon dioxide concentration; ETO_2 = end tidal oxygen concentration; LVEF = left ventricular ejection fraction; MVO_2 = mixed venous oxygen saturation; PAH = pulmonary arterial hypertension; PAP = pulmonary arterial pressure; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PVR = pulmonary vascular resistance; SpO_2 = arterial blood oxygen saturation; TAPSE = tricuspid annular plane systolic excursion; TEAE = treatment emergent adverse event; TP = treprostinil palmitil; TPIP = treprostinil palmitil inhalation powder; TRE = treprostinil; TVR = tricuspid valve regurgitation; t_{max} = time of maximum observed concentration following drug administration; $t_{1/2}$ = elimination half-life; Vd/F = apparent volume of distribution at terminal phase; VCO_2 = carbon dioxide production

3.1. Exploratory Objectives and Endpoints for the Optional Extended Use Treatment Period

Objectives	Endpoints
Exploratory	Exploratory
• To evaluate the safety and tolerability of TPIP in participants with PAH	• Frequency of TEAEs during EUT

• To assess the effect of TPIP on exercise capacity	• Change from Baseline in 6MWD distance at EUT Baseline to EUT Week 16

6MWD = 6-minute walk distance; EUT = extended use treatment period; PAH = pulmonary arterial hypertension; TEAE = treatment emergent adverse event; TPIP = treprostinil palmitil inhalation powder

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2a, open label, non-randomized study to assess the safety, tolerability, PD effects and PK of TPIP administered to participants with WHO Group 1 PH (PAH). This is the first patient study of TPIP. Each participant will receive a single dose of TPIP. The first participant will receive a dose containing 112.5 µg of TP. The TP dose level for each subsequent participant will be determined following review and adjudication of all available safety, PK, and PD data from the previous participant(s) by the SRC (Section 10.1.7). There is an optional extended-use period for 16 weeks in participants who have completed the core, single-dose period.

This is a "proof of mechanism" study designed to investigate the following:

1. The safety and tolerability of TPIP in participants with PAH,
2. The relationship between the PK and PD effects of TPIP in participants with PAH, and
3. The duration of the PD effects of a single dose of TPIP in participants with PAH.

The cardiopulmonary and overall functional status of participants with PAH can be labile and medical instability can develop quickly. The study is designed to provide maximal safety and minimal risk to participants. As such, there considerable flexibility built into the protocol to allow Investigator discretion with the frequency, timing, and/or conduct of PD and PK assessments to ensure participant safety. Because the study requires an overnight inpatient treatment period, institutional requirements for elective inpatient admissions, which may vary from site to site, will be followed.

For individual participants, the study will consist of an outpatient screening period lasting up to 30 days. The inpatient treatment period will start on Study Day 1 and is expected to last overnight into Study Day 2. Outpatient PK sampling and safety follow-up at 48 (± 4) hours post TPIP dose will extend into Study Day 3. A remote safety follow-up visit is scheduled for Study Day 30 (± 2 days). The 48 hour PK visit will also include safety assessments including ECG, clinical laboratory evaluations, vital signs, physical examination, and AE collection (Table 1). The safety follow-up period will conclude with a remote (telephone or telemedicine) visit on Study Day 30 (± 2 days). The screening, treatment, and follow-up periods for the core, single-dose portion of the study are expected to be 62 days or less. An EUT period of 16 weeks will be optional for participants that complete the single-dose period, followed by a 30 day follow-up (± 3 days). This extends study participation to 142 days after enrollment in the EUT period.

4.1.1. Screening Period

The initial screening period will be up to 30 days. Required screening assessments are shown in Table 1. Participants who fail one or more screening assessments may be re-screened once at the Investigator's discretion in order to meet study entry criteria. See Section 5.4 for additional information regarding participants who fail screening and/or are re-screened.

Participants who enter the optional EUT period more than 30 days after beginning the single-dose period (e.g., beyond the initial 30 day follow-up period) will be screened to ensure they continue to satisfy inclusion and exclusion criteria. Extended use treatment period screening assessments are shown in Table 5.

4.1.2. Inpatient Treatment Period

4.1.2.1. Baseline Procedures and Assessments

The inpatient treatment period will be on Study Days 1 and 2. The participant may be required to undergo pre-admission assessments required by the Institution for elective admission, for example testing for common infectious pathogens. Signature of institutional elective admission documents and consents to procedures may be required. Data from required institutional assessments and consents will not be routinely collected as part of study data unless they pertain to a relevant AE or study endpoint.

Participants will be admitted to an inpatient care setting such as an ICU, cardiac catheterization laboratory or other similar setting. They will have Baseline laboratory and safety assessments as shown in Table 2. An RHC will be placed for Baseline assessment of cardiopulmonary hemodynamics prior to TPIP administration and intermittent assessments of cardiopulmonary hemodynamics for 24 hours following TPIP administration. Institutional procedures and protocols for placement, care, monitoring, and removal of the RHC will be carried out but will not be collected as study data unless relevant.

Some procedures and assessments for exploratory endpoints may not be offered at all sites. Participants will be asked to give informed consent only to those procedures that are being conducted by their Investigator at their site. These procedures include the following:

- Transthoracic echocardiogram at Baseline and during a 2 to 8 hour window after TPIP administration (Table 4).
- Pulmonary computerized tomography (CT) scan at Baseline and during a 4 to 8 hour window after TPIP administration (Table 4).
- Resting respiratory gas exchange assessment at Baseline and intermittently after TPIP administration for up to 24 hours (Table 4). Resting respiratory gas exchange assessments will be standardized, with all participating investigators using similar equipment and procedures.

For example, an Investigator who is doing only RHC and resting respiratory gas exchange assessments for this study will obtain informed consent for those procedures only and will not offer or ask the participant for informed consent for transthoracic echocardiogram or pulmonary CT scan as part of this study.

Following completion of all Baseline assessments, including Baseline blood draws for PK and PD biomarkers (Table 3), the prescribed single dose of TPIP will be administered (Table 2).

4.1.2.2. Post-TPIP Administration

Following TPIP administration, participants will have intermittent safety, clinical laboratory, PK, and PD assessments, as specified in the SoA (Table 2, Table 3, and Table 4). The study is designed to allow maximum flexibility for interventions and assessments at the discretion of the Investigator and institutional policies and procedures to ensure participant safety. At any time, the Investigator has the option to discontinue assessments for participant safety or tolerability reasons. Additional laboratory and/or hemodynamic assessments may be performed as deemed necessary for participant safety. Following completion of scheduled events, the Investigator has the option of continued laboratory and/or hemodynamic monitoring as deemed appropriate for participant safety.

If, in the interest of participant safety, the Investigator omits scheduled assessments/procedures or performs additional assessments/procedures, the reason for doing so must be reported on the CRF as an AE in order to avoid a protocol violation.

Following completion of protocol-required assessments and removal of the RHC, the participant will be discharged from the inpatient setting when deemed safe by the Investigator. Investigator and institutional usual care protocols for participant discharge and follow-up for an RHC procedure will apply.

4.1.2.3. Post-discharge Outpatient Visits for PK Sampling and Safety Follow-up

The participant will be required to return as an outpatient for the 48 (± 4) hour post-TPIP administration PK sample. Additional safety assessments such as ECG, physical examination, vital signs, AE collection, and clinical laboratory evaluations will be completed at the 48 hour visit. Female participants who are women of child-bearing potential (WOCBP) will be given a self-administered pregnancy test kit with instructions to self-administer the test and report the results on the day of the Study Day 30 safety follow-up visit (Section 4.1.3).

4.1.3. Safety Follow-up

A remote (telephone call or telemedicine) safety follow-up visit is scheduled for Study Day 30, at which time participants who are WOCBP will also be asked to report the results of the self-administered pregnancy test they were given at the 48 hour post-TPIP follow-up visit (Section 4.1.2.3, Table 1).

4.1.4. Optional Extended Use Treatment Period

All participants will be allowed to enter the optional 16 week EUT period after the completion of the inpatient treatment period and final PK sample collection. Entry into the optional EUT period will be at participant and Investigator discretion. A gap between the inpatient treatment period and EUT period is expected, but not required, and can be up to 6 months.

After collection of the final PK sample, all participants will be allowed optional continued access to IMP for 16 weeks (includes a 3-week titration period) from first administration in the EUT period. At the Investigator's discretion, participants may undergo a study drug taper for up to 2 weeks after the Week 16 visit to help facilitate a safe withdrawal from study drug.

Participants will be screened to ensure they meet inclusion and exclusion criteria if they enter the EUT period more than 30 days after beginning the single-dose period (e.g., beyond the initial 30 day follow-up period) (Table 5).

Participant in-clinic study visits will be scheduled for EUT Baseline (EUT Day 1), EUT Week 2, EUT Week 3, EUT Week 5, EUT Week 10, and EUT Week 16.

The CT scan will be performed according to instructions provided by the CT scan vendor.

There will be a second safety follow-up visit 30 days (± 3 days) after EUT Week 16 for participants who elect to enter the EUT period.

4.1.5. Open-label Extension Study

When available, participants may be eligible to enroll in a separate OLE study that will have a duration of approximately 2 years. Details of the planned OLE study will be provided in a separate protocol.

4.2. Scientific Rationale for Study Design

The study is designed to understand the safety and acute PK and PD effects of TPIP in participants with PAH, the intended patient population. Intensive monitoring via RHC in an appropriate inpatient setting is essential to understand how TPIP affects cardiopulmonary hemodynamics and to elucidate relationships between dose, PK, and PD effects. Some assessments and study activities for exploratory endpoints are considered optional depending on Investigator preference and/or based on study site capabilities and procedures (Table 4).

4.3. Justification for Dose

4.3.1. Inpatient Treatment Period (Single-dose)

Treprostinil palmitil has been previously studied in healthy volunteer participants as a liquid suspension for inhalation (TPIS) and has now been formulated as a dry powder for oral inhalation (TPIP). Data from pre-clinical pharmacology and safety studies supported the initiation of human studies with TPIS. Preclinical studies in rats and dogs showed that the plasma kinetics of TRE and TP after dosing with TPIP are similar to those of TPIS. Additional clinical PK and safety data from healthy participants after SAD and MAD dosing with TPIP supported the chosen study design and dose. For further information on the non-clinical pharmacology and safety studies of TPIS and TPIP, please refer to the Investigator's Brochure.

The current study utilizes the clinical experience of TPIS from Study INS1009-101 in healthy volunteer participants and the INS1009-102 SAD/MAD study of TPIP in healthy volunteer participants. In Study INS1009-101, doses of TPIS were administered in multiples of 85 µg TP to include 170 µg (2 × 85 µg) and 340 µg (4 × 85 µg) of TP. The systemic exposure for TRE at 340 µg TP was low (AUC < 2.5 ng*h/mL) with an elimination $t_{1/2}$ of approximately 7 hours.

Data from the INS1009-102 SAD/MAD study of TPIP reinforced the study design and informed maximum dosage for the optional extended use portion of the study (Section 4.3.2). In the first SAD portion of INS1009-102 (SAD1), 18 participants were randomized to 1 of 3 TP dose levels

of TPIP: 112.5 µg, 225 µg, or 450 µg of TP (6 participants at each dose). Treprostinil peak concentrations in the SAD portion were attained at 1.5 to 3 hours post-dose; C_{max} and AUC were dose-dependent and approximately proportional to the increase of dose; and elimination $t_{1/2}$ was 8.7 to 11.6 hours. Total treprostinil exposure (AUC) of treprostinil was found to be dose proportional following a single administration of TPIP across the dose range of 112.5 µg to 675 µg.

Administration of TPIP will be via inhalational dry powder packaged in single actuation capsules. Each capsule contains 7.5 mg of dry powder, containing 112.5 µg of the TP prodrug, the molar equivalent of 71 µg of TRE. Approximately 85 µg of TP (54 µg of TRE equivalent) will be emitted from the dry powder inhalation device. This is comparable to a single administration of Tyvaso for patients with PAH with the target dose being 54 µg QID. Single doses of up to 90 µg of Tyvaso have been administered in clinical studies of healthy volunteer participants (Tyvaso Package Insert, 2017).

Each participant will receive a single dose administration of TPIP. A TPIP dose containing 112.5 µg of TP will be given to the first participant in Study INS1009-201. All available data (PD, PK, safety) from the first participant will be assessed and evaluated by the SRC. Following this evaluation, the SRC will determine if it is safe to continue the study, the TPIP dose level and any changes to safety PD and PK assessments for the second participant (Figure 3). This process will be repeated using the total accrued data of all completed participants prior to determining the TPIP dose for each subsequent participant. There will be no simultaneous dosing of inpatient participants; each participant will be treated as an individual case for evaluation. The TP dose level for each subsequent participant may be increased, held stable or lowered, depending on the accumulating data from previous participants up to a maximum of 675 µg. TPIP dosing may also be stopped at any dose level as determined by the SRC.

4.3.2. Optional Extended Use Treatment Period

Selection of once-daily inhalation of TPIP at 80 – 640 µg was based on clinical PK and safety data from healthy participants, predicted efficacious dose levels using pre-clinical data, safety margin from rat and dog NOAEL doses, and Tyvaso® clinical experience.

In Phase 1 studies, TRE PK was linear, and the systemic exposure was dose proportional. Single doses of up to 675 µg and multiple doses of up to 225 µg TPIP QD for 7 days were generally well tolerated. Most AEs observed were mild in severity and consistent with the safety profile of other prostanoid therapies.

Based on exposures following a single dose of TPIP 675 µg in Study INS1009-102, TRE exposures in this study are not anticipated to exceed those following administration of the currently approved treprostinil product, Remodulin®. Treprostinil exposures following a continuous IV infusion of 10 ng/kg/min Remodulin (C_{max} 1,470 pg/mL; AUC 25,690 pg*h/mL) are reported to be 2.1-fold and 4.7-fold higher, respectively, than those observed following administration of TPIP 675 µg (C_{max} 717 pg/mL; AUC 5,480 pg*h/mL)(Laliberte et al., 2004). Minimal accumulation was observed following repeat doses of TPIP 225 µg QD for 7 days, and since a lower maximum dose (640 µg) will be used in the extended use portion of this study,

TRE exposures are expected to be lower than those observed following single doses of TPIP 675 µg in Study INS1009-102.

Based on the findings above, the TPIP dose will range from 80 µg to 640 µg QD in this treatment period.

4.4. Study Completion

A participant will be considered to have completed the study if he/she has completed the Study Day 30 safety follow-up (shown in Table 1) and has not elected to enter the optional EUT period. A participant who has entered the optional EUT period will be considered to have completed the study if he/she has completed the EUT period safety follow-up (EUT Day 142). The study will be considered completed on the date of the last safety follow-up of the last participant in the study.

5. STUDY POPULATION

The study is expected to recruit approximately 6 to 10 participants at up to 7 centers with appropriate inpatient facilities in the United States. Eligible participants must have clinically stable disease of mild to moderate severity, with good to moderate functional status. Participants may not be taking more than 2 medications from the following classes:

- Endothelin receptor antagonists (eg ambrisentan, bosentan, macitentan),
- Phosphodiesterase type 5 inhibitors (eg sildenafil, tadalafil)
- Guanylate cyclase stimulator (eg riociguat)

It is expected that the site will recruit appropriate potential participants according to the criteria in Section 5.1 and Section 5.2. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

The study inclusion and exclusion criteria include thresholds of selected RHC and ECG parameters that must be met at Baseline or the participant will not be considered eligible for the study. In this case, the participant is to be reported as a Screen Failure (Section 5.4).

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if they meet all of the following criteria[a]:

Age:
1. Participant must be ≥ 18 years of age at the time of signing the informed consent.
Type of Participant and Disease Characteristics
2. Participants must have a diagnosis of WHO Group 1 PH (PAH) with the following characteristics (Galie et al., 2016): a. Etiology of idiopathic, heritable, drug/toxin-induced or connective tissue disease (CTD)-related PAH; b. Right heart catheterization within the last 3 years with the following hemodynamic findings: - Mean pulmonary arterial pressure (mPAP) > 20 mmHg at rest, - Pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg, and - Pulmonary vascular resistance (PVR) of ≥ 3 Wood Units (WU) 3. PAH diagnosis for at least 1 year 4. New York Heart Association (NYHA)/WHO Functional capacity Class I-III 5. No change in pulmonary hypertension medications (e.g., ambrisentan, bosentan, macitentan, sildenafil, tadalafil, riociguat) or dosage for at least 90 days prior to Screening. 6. No change in diuretic use or dosage for at least 30 days prior to Screening

7. Documented predicted percent forced vital capacity (FVC) > 70% within 1 year of Screening. If not available, pulmonary function testing will be performed at Screening (Table 1).
8. At least 2 of the following European Respiratory Society/European Society for Cardiology (ERS/ESC) low risk criteria:
    a. NT-pro-BNP concentration < 300 ng/L within 6 months of Baseline (if not available will be obtained at Screening, Table 1).
    b. Historical documentation of 6- minute walk distance (6MWD) > 440 meters within 6 months prior to Baseline. If not available will obtain 6MWD test at Screening (Table 1).
    c. Right atrial pressure (RAP) < 8 mmHg within 1 year prior to Baseline
    d. Cardiac Index (CI) ≥ 2.5 L/min*m^2 or mixed venous oxygen saturation (MVO_2) > 65% within 1 year prior to Baseline
9. Right heart catheterization at Baseline with the following hemodynamic findings:
    a. Mean pulmonary arterial pressure (mPAP) > 20 mmHg at rest,
    b. Pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg, and
    c. Pulmonary vascular resistance (PVR) of ≥ 3 Wood Units (WU)

Weight

10. Body mass index (BMI) within the range 19.0 - 32.0 kg/m^2 (inclusive).

Sex and Contraceptive/Barrier Requirements

11. Male participants: Male participants and their female partners of childbearing potential must agree to use highly effective contraception from Study Day 1 to at least 90 days after dosing.
12. Female participants: Women of child-bearing potential (WOCPB, defined as premenopausal, not surgically sterile for at least 3 months prior to Screening) must use a highly effective contraception method and agree to be tested for pregnancy from at Screening, Baseline, and 30 days after dosing.

See Section 10.4 for contraceptive guidance.

Informed Consent

13. Capable of giving signed informed consent as described in Section 10.1.5 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

[a] Please note that participants who enroll in the optional EUT period beyond the initial 30 day follow-up period will be screened to confirm that they still meet inclusion/exclusion criteria. Please refer to Table 5.

5.2. Exclusion Criteria

Participants are excluded from the study if they meet any of the following criteria[a]:

Medical Conditions

1. Any PH other than idiopathic, hereditary, drug/toxin-induced, or connective tissue disease (CTD) associated PAH (e.g., congenital heart disease-associated PAH, portal hypertension-associated PAH, PH belonging to Groups 2 through 5)
2. Allergy, or documented hypersensitivity or contraindication, to the ingredients of treprostinil palmitil inhalation powder (TPIP) or treprostinil (TRE).
3. Previous intolerance to prostacyclin analogs or receptor agonists (e.g., selexipag) per Investigator discretion
4. History of anaphylaxis or previously documented hypersensitivity reaction to any drug per Investigator discretion
5. QTcF interval > 480 ms on resting ECG at Baseline
6. History of heart disease including left ventricular ejection fraction (LVEF) ≤ 40% or clinically significant valvular, constrictive, or atherosclerotic heart disease (myocardial infarction, etc)
7. Abnormal renal function (estimated glomerular filtration rate < 30 mL/min/1.73m^2) at Screening.
8. Active liver disease or hepatic dysfunction manifested as:
    a. Elevated liver function test results (ALT or AST > 2 × ULN) at Screening
    b. Bilirubin > 1.5 × ULN (isolated bilirubin > 1.5 × ULN; ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%) at Screening.
    c. Known hepatic or biliary abnormalities, not including Gilbert's syndrome or asymptomatic gallstones at Screening.
9. History of HIV infection/positive HIV serology test result at Screening.
10. History of active/chronic Hepatitis B or C/ positive hepatitis B or C serology test result at Screening
11. History of abnormal bleeding or bruising.
12. Known or suspected immunodeficiency disorder, including history of invasive opportunistic infections (e.g., tuberculosis, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis) despite infection resolution, or otherwise recurrent infections of abnormal frequency, or prolonged infections suggesting an immune-compromised status, as judged by the Investigator.

13. Active and current symptomatic infection by SARS CoV 2. Additional COVID 19 restrictions per institutional guidelines (See also Section 10.1.3.1.3) 14. Participants with current or recent (past 4 weeks) lower respiratory tract infection (may be re-screened at appropriate time (Section 5.4) 15. History of malignancy in the past 5 years, with exception of completely treated in situ carcinoma of the cervix and completely treated non-metastatic squamous or basal cell carcinoma of the skin.
Concomitant Therapy
16. Participants receiving triple combination therapy for PAH consisting of endothelin receptor agonists, phosphoesterase type 5 inhibitors, and guanylate cyclase stimulators (riociguat). 17. Participants receiving prostanoids/prostacyclin agonists 18. Participants receiving potent CYP2C8 inhibitors, such as gemfibrozil 19. Other prior/concomitant therapies are allowed/disallowed at the Investigator's discretion
Prior/Concurrent Clinical Study Experience
20. Have participated in any other interventional clinical studies within 30 days of Baseline
Diagnostic assessments
21. Any clinically significant abnormal laboratory, value, test result, or physical examination finding at Screening; diseases or diagnoses/disorders that, in the opinion of the Investigator, may put the participant or others at risk by participating in the study, interfere with the participant's treatment and assessment, or influence the results of the study; or have compliance issues with the study.
Other Exclusions 22. Current or history of substance and/or alcohol abuse per Investigator assessment 23. Current user of cigarettes or e-cigarettes 24. Pregnant or breastfeeding.

[a] Please note that participants who enroll in the optional EUT period beyond the initial 30 day follow-up period will be screened to confirm that they still meet inclusion/exclusion criteria. Please refer to Table 5.

5.3. Lifestyle Considerations

No lifestyle restrictions are required.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study because they did not meet all inclusion criteria or meet one or more exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once at the Investigator's discretion. If a participant can be rescreened, the PI is to consult with the Medical Monitor to determine whether some or all of the screening assessments must be repeated. Rescreened participants will sign a new ICF and will be assigned a new participant number.

5.5. Criteria for Temporarily Delaying Inpatient Treatment Period

Following successful screening and meeting of study eligibility criteria, the inpatient treatment period and RHC procedure must be scheduled without delay.

The scheduled treatment period may be temporarily delayed no longer than 28 days by the Investigator in consultation with the Medical Monitor for valid reasons. Examples of valid reasons for delaying the treatment period may include such things as a life event for the participant (eg death in the family), local public health emergency (e.g., COVID 19 outbreak), site facility issues (e.g., catheterization lab or ICU bed availability), or pending TPIP dosing directives from the SRC.

A temporary delay in the scheduled inpatient treatment period for a valid reason may result in previously met Inclusion Criteria that rely on a time window to be not met (e.g., 6MWD falls outside the 6 months prior to Baseline window). This is not considered to be a Screen Failure. In this case, the Investigator should consult with the Medical Monitor to identify which screening tests need to be conducted or repeated to ensure that the participant meets study inclusion criteria and can safely participate in the study.

Deterioration of the participant's medical condition is not a valid reason to delay start of the inpatient treatment period. In some cases, delaying the inpatient treatment period may cause the participant to meet one or more exclusion criteria (e.g., participant develops a lower respiratory infection). In this case the participant should be considered a Screen Failure and Section 5.4 applies.

6. STUDY IMP AND CONCOMITANT THERAPY

Study IMP is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study IMP Administered

6.1.1. Inpatient Treatment Period (Single Dose)

A single dose of TPIP will be used in the inpatient treatment period. Each TPIP capsule contains 7.5 mg of dry powder, containing 112.5 µg of the TP prodrug. A dose may consist of a single capsule or of multiple capsules administered in succession.

Name of Treatment	Dose	Supplied Formulation	Route and Frequency of Administration
Treprostinil palmitil inhalation powder (TPIP)	One or more single actuation capsules	Single actuation capsules containing 112.5 µg TP per 7.5 mg powder	Inhalation; single dose after Baseline assessments
Treprostinil palmitil inhalation powder (TPIP)	One or two single actuation capsules (80 µg, 160 µg, 240 µg, 320 µg, 400 µg, 480 µg, or 640 µg)	Dry powder single actuation capsules containing 80 µg, 160 µg, or 320 µg	Inhalation; single dose after Baseline assessments

QD = once daily

6.1.2. Optional Extended Use Treatment Period

The IMP used in the EUT period will be capsules containing 1 of 3 dosage strengths of TPIP (80 µg, 160 µg, or 320 µg). IMP should be taken around the same time every day. Administration of IMP will be via inhalational dry powder packaged in single actuation capsules. One or 2 capsules will be administered for each dose. Administration of 2 capsules should be done sequentially. Each TPIP capsule contains 8 mg, 16 mg, or 32 mg of dry powder containing 80 µg, 160 µg, or 320 µg of the TP prodrug, respectively.

Name of Treatment	Dose	Supplied Formulation	Route of Administration
Treprostinil palmitil inhalation powder (TPIP)	One or two single actuation capsules (80 µg, 160 µg, 240 µg, 320 µg, 400 µg, 480 µg or 640 µg QD)	Dry powder single actuation capsules containing 80 µg, 160 µg, or 320 µg	Inhalation (QD)

QD = once daily

6.1.3. Medical Devices

In the planned clinical study, the TPIP will be administered by oral inhalation using a Plastiape capsule-based Dry Powder Inhaler (RS 01 Mod 7). A Type III Drug Master File is filed at the US FDA and the RS01 inhaler is classified as a Class I medical device. The Instructions for Use of the device document is provided separately as an Appendix to the Pharmacy Manual.

All device deficiencies (including malfunction, use error, and inadequate labeling) shall be documented and reported by the Investigator throughout the clinical investigation (Section 8.3.7) and appropriately managed by Insmed.

6.2. Preparation/Handling/Storage/Accountability

Insmed Incorporated will provide the Investigator and clinical unit with adequate quantities of TPIP capsules. For 112.5 µg doses, TPIP-filled HPMC capsules will be delivered in HDPE bottles overwrapped with an aluminum pouch, containing a sachet of desiccant to prevent moisture ingress. For 80 µg, 160 µg, or 320 µg doses, HDPE bottles will be closed with the desiccant placed inside the bottle, and induction sealed. The powder will be administered by oral inhalation using a Plastiape capsule-based Dry Powder Inhaler.

6.2.1. Inpatient Treatment Period (Single-dose)

Directions for preparation and administration of the TPIP dose to the participant are provided in a separate document as an Appendix to the Pharmacy Manual for the single-dose Inpatient Period.

All study IMP must be stored according to the labeled instructions in a secure cabinet or room with access restricted to necessary clinic personnel. The site will be required to keep a temperature log to establish a record of compliance with storage conditions. Current stability data supports the shelf life assigned to TPIP when stored at 2 to 8 °C.

- The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study IMP received and any discrepancies are reported and resolved before use of the study IMP.
- Only participants enrolled in the study may receive TPIP and only authorized site staff may supply or administer it. All TPIP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
- The Investigator, institution, and/or pharmacist or designee is responsible for study IMP and dosing devices accountability, reconciliation, and record maintenance (e.g., receipt, reconciliation, and final disposition records).
- Study IMP and dosing device accountability records will be maintained for all clinical supplies. All transactions will be recorded on the drug and dosing device accountability records including shipment receipts and study participant doses. All transactions will be recorded on a real-time basis.

- The Investigator/site will maintain detailed documentation of the number and identification of bottles and dispensing units of TPIP with copies of these documents to be provided to Insmed at the end of the study. All used and unused study IMP and dosing devices will be maintained by the site until inventoried by the study monitor. Upon completion of the study IMP and dosing device inventory by the study monitor, used and any unused study IMP and dosing devices will be disposed of in accordance with instructions provided to sites and according to site destruction policies. Documentation of destruction must be provided to Insmed.
- Further guidance and information for the final disposition of unused study IMP supplies can be obtained from Insmed.

6.2.2. Optional Extended Use Treatment Period

Directions for preparation and administration of IMP to the participant in-clinic are provided in the Pharmacy Manual for the optional EUT period. Directions for preparation and administration of IMP for home use will be provided to the participants.

Only participants enrolled in the study may receive IMP, and only authorized study personnel may supply IMP. All IMP must be stored according to the labeled instructions with access restricted to necessary clinic personnel. The site will be required to keep a temperature log to establish a record of compliance with storage conditions. Refer to the Pharmacy Manual for the optional EUT period for shelf-life and storage conditions.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for IMP and dosing devices accountability, reconciliation, and record maintenance (e.g., receipt, reconciliation, and final disposition records). Directions for storage, handling, accountability, and destruction are provided in the Pharmacy Manual for the optional EUT.

6.3. Measures to Minimize Bias: Randomization and Blinding

Not applicable.

6.4. Study Intervention Compliance

6.4.1. Inpatient Treatment Period (Single Dose)

Study participants will receive the TPIP dose directly from the Investigator or designee, under medical supervision, in an appropriate inpatient setting. The date and time of the dose administered will be recorded in the source documents. The dose of TPIP and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the TPIP.

6.4.2. Optional Extended Use Treatment Period

At each in-clinic visit, participants will be dispensed adequate IMP to allow for daily dosing. When participants are dosed at the site, IMP administration will be overseen by study site personnel. The date and time of each dose self-administered in the clinic will be recorded in the

source documents. The dose of IMP and study participant identification will be confirmed at the time of dosing by a member of the study site personnel.

When participants administer IMP at home, compliance with IMP will be assessed at each in-clinic visit. Participants will record their daily dose on paper dosing diaries. Compliance will be assessed by direct questioning, review of participant dosing diaries, and counting of returned capsules during the site visits. Participants will return unused capsules and used study capsules and devices to the study site at each in-clinic visit. Participants who undergo a study drug taper will return unused capsules and used capsules and devices to the study site at a follow-up visit. Unused capsules should be returned in the bottle they were dispensed in. Deviation(s) from the prescribed dosage regimen should be recorded.

A record of the quantity of capsules dispensed to and administered by each participant must be maintained and reconciled with study drug logs and participant dosing diaries. Study drug start and stop dates, including dates for study drug interruptions and/or dose reductions will also be recorded.

6.5. Dose Modification

Dose modification is part of the study design and is described in detail in Section 4.3 and Section 1.3.2.

6.6. Continued Access to Study Intervention After the End of the Study

Not applicable.

6.7. Treatment of Overdose

An overdose is defined as the participant receiving any TPIP in excess of their assigned dose as predetermined by the SRC (Section 4.3). An overdose itself is not an AE. However, if the overdose results in clinical signs and symptoms, it requires expedited reporting as if it is an SAE. The Investigators must refer to the relevant documents for detailed information regarding warnings, precautions, contraindications, AEs, and other significant data pertaining to the study IMP. Such documents may include, but are not limited to, the Investigator's brochure.

In the event of an overdose, the Investigator must:

- Contact the Medical Monitor within 24 hours.
- Evaluate the participant to determine, in consultation with the Medical Monitor, how to proceed with treatment period procedures and assessments.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until TP or TRE is likely to be sufficiently metabolized and/or excreted and/or can no longer be detected systemically. The frequency and duration of plasma sampling from the last dose of TPIP must be determined by the Investigator in conjunction with the study team and Medical Monitor.
- The overdose must be fully documented (e.g., quantity of the excess dose, duration of the overdose, how it happened) in the CRF.

6.8. Concomitant Therapy

Any medications, treatments, or therapies that the participant is receiving at Baseline (Study Day 1) or receives during the study (Study Day 1 through end of study [EOS]) are considered concomitant therapy and will be collected and documented in the study CRF.

Documentation includes the name of the therapy, with the reason for use, the dates of administration including start and end dates, and dosage information including dose and frequency.

Prior medications are those medications taken before the first dose of study IMP. A medication that starts prior to first dose but continues after the first dose of study IMP is classified both in prior and concomitant medications. Any procedures performed from Day 1 through EOS are considered concomitant procedures and will be collected and documented in the study CRF.

The Medical Monitor must be contacted if there are any questions regarding concomitant or prior therapy.

For participants who enroll in the EUT period, new concomitant therapy for the period from the single-dose Study Day 30 follow-up until the enrollment in the EUT will be collected during participant's screening for the EUT.

7. DISCONTINUATION OF STUDY IMP AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study IMP

7.1.1. Single-dose Period

This is a single dose period; not applicable.

7.1.2. Optional Extended Use Treatment Period

If study drug is permanently discontinued, the participant will be encouraged to participate in their remaining study visits. See Table 6 for data to be collected at the time of discontinuation of IMP and follow-up. If a participant discontinues the study and needs to be started on another PAH medication, the Investigator should contact the Medical Monitor.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons.

At the time of discontinuing from the study after study drug administration, if possible, an early discontinuation evaluation should be conducted to maximize participant safety. This final evaluation and the reason for participant withdrawal must be documented in the CRF.

The participant will be permanently discontinued both from the study drug and from the study at that time.

If the participant is discontinued from the study due to an SAE, the Investigator will follow the participant until the Investigator deems that the SAE has resolved or stabilized.

The Investigator may withdraw the participant from the study due to absence of a PD response to TPIP. Lack of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the PK and PD assessments.

If the participant withdraws consent for disclosure of future information, Insmed may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled follow-up visits and is unable to be contacted by the study site.
The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of

maintaining the assigned visit schedule and ascertain whether or not the participant wishes to continue in the study.

- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts must be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered lost to follow-up and to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants, including those who did not get study IMP. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Insmed personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1.13.2).

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in Table 1, Table 2, Table 3, Table 4, Table 5, Table 6.

All screening evaluations must be completed and reviewed to confirm that potential participants meet eligibility criteria prior to scheduling the study RHC procedure and inpatient admission. The RHC procedure and inpatient admission must be scheduled for as soon as possible once the participant's eligibility for the study is confirmed by screening. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (e.g., previous RHC, previous echocardiogram, previous 6MWD test) and obtained before signing of the ICF may be utilized for screening or Baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frames defined in the inclusion and exclusion criteria in Section 5.

For participants who do not elect to enter the EUT period, the maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required is expected to be approximately 140 mL and will not exceed 200 mL. Approximately 80 mL will be required for PK sampling over 48 hours and approximately 20 mL for biomarker sampling. Safety and screening blood samples will require approximately 20 to 30 mL. Blood loss from the RHC procedure is anticipated to be negligible.

For participants who do elect to enter the optional EUT period within the 30 day follow-up window in the single-dose period, there is no anticipated blood collection. For participants who elect to enter the optional EUT period after the 30 day follow-up in the single-dose period, Safety and screening blood samples will require approximately 20 to 30 mL. Blood loss from the RHC procedures is anticipated to be negligible.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples at the Investigator's discretion.

At any time, the Investigator has the option to discontinue assessments for participant safety or tolerability reasons. Additional laboratory, PK, and/or hemodynamic assessments may be performed as deemed necessary for participant safety. Following completion of scheduled events, the Investigator has the option of continued laboratory and/or hemodynamic monitoring as deemed appropriate for participant safety. If, in the interest of participant safety, the Investigator omits scheduled assessments/procedures or performs additional assessments/procedures, the reason for doing so must be reported on the CRF as an AE in order to avoid a protocol violation.

8.1. Pharmacodynamic Assessments

The results of each individual participant's PD assessments will contribute to the dosing decision for the next participant (Section 4.3).

8.1.1. Required PD Assessments with RHC

PVR, CO, PAP (mean), RAP (mean), RVP, hemoglobin, and MVO_2 will be measured via the RHC at the time points indicated in the SoA (Table 2). Oxygen consumption is part of the MVO_2 calculation and may be measured or estimated at 125 mL O_2 per square meter (m^2) of body surface area (BSA). These or other parameters may be optionally measured at other time points or omitted to ensure participant safety at the Investigator's discretion. If measurements are missed, or additional measurements are taken for safety purposes, the reason must be documented as an AE in the CRF.

Institutional procedures for insertion, care, monitoring, and removal of the RHC will be followed. Specific technique and procedures for measurement of PVR, CO, PAP, RAP, RVP, hemoglobin, oxygen consumption, and MVO_2 are provided in a separate Procedure Guide.

8.1.2. Required Non-invasive PD Assessments

Systemic blood pressure (mmHg) may be measured by inflatable cuff. Systemic blood pressure must include 3 values: systolic, diastolic, and mean arterial pressure. Arterial oxygen saturation (SpO_2, %) and heart rate (beats per minute) may be measured by pulse oximeter.

8.1.3. Resting Respiratory Gas Exchange Assessments

Specific measurements for resting respiratory gas exchange assessment include changes from Baseline in respiratory rate (breaths per minute), minute ventilation (mL per minute), carbon dioxide production (VCO_2, mL per minute), end tidal oxygen concentration (ETO_2, %), and end tidal carbon dioxide concentration ($ETCO_2$, %). The gas exchange parameters will be monitored at the same time points as the PD assessments in Section 8.1.1 (Table 2, Table 4). Specific instructions for resting respiratory gas exchange assessment procedures and measurements are provided in a separate Procedure Guide.

8.1.4. Transthoracic Echocardiogram Assessments

Transthoracic echocardiogram is to be performed at Baseline and during a 2-8 hour window following TPIP administration (Table 4). Specific instructions for echocardiographic procedures and measurements are provided in a separate Procedure Guide.

8.1.5. Pulmonary CT Scan

8.1.5.1. Single-dose Period

Pulmonary CT scanning to assess pulmonary vasculature and blood flow is scheduled for Baseline and during a 4-8 hour window following TPIP administration (Table 4). Specific requirements and instructions for pulmonary CT scanning and required parameters are provided in a separate Procedure Guide.

8.1.5.2. Optional Extended Use Treatment Period

An optional pulmonary CT scan may be performed at first visit (±3 days) and at EUT Week 16 (±3 days) in the optional EUT period, as indicated in Table 6. The CT scan will be performed according to instructions provided by the CT scan vendor.

8.2. Safety Assessments

Evaluation of the safety and tolerability of single doses of TPIP in participants with PAH is the primary objective of this study. Planned time points for all safety assessments are provided in Table 1 and Table 2. The results of the individual participant's safety assessments during and after TPIP administration will contribute to the dosing decision for the next participant (Section 1.3.2). Participants who elect to enter the optional EUT period will also be monitored for safety, as listed in Table 6.

8.2.1. Physical Examinations

Screening: The physical examination must focus on those areas that determine the individual participant's eligibility to participate in the study and do so safely at the Investigator's discretion and will be documented accordingly.

Baseline: The physical examination must focus on the participant's fitness for the study procedures and TPIP administration.

Discharge: The physical examination must focus on the participant's fitness to be safely discharged to home from the inpatient setting. Special attention must be paid to assessment of any new or ongoing AEs.

Follow-up: The in-person physical examination must focus on participant safety and assessment of AEs that were ongoing at discharge or have occurred since discharge.

8.2.2. Vital Signs

8.2.2.1. Single-dose Period

Temperature, heart rate, respiratory rate, and blood pressure at screening and 48 hour post-TPIP administration follow-up will be per the Investigator's usual outpatient practice and documented accordingly.

Baseline and post-TPIP administration: Changes from Baseline in heart rate, respiratory rate, and systemic blood pressure are PD endpoints as well as safety variables and must be measured as specified (Section 8.1). Vital signs outside of PD endpoints will be monitored per the inpatient unit's usual practices.

8.2.2.2. Optional Extended Use Treatment Period

Changes in heart rate, respiratory rate, body temperature, and systemic blood pressure will be monitored as described in Table 6. Vital signs will be measured at Extended Use

Screening/Baseline (EUT Day 1), EUT Week 2, EUT Week 3, EUT Week 5, EUT Week 10, and EUT Week 16 and at the Early Discontinuation visit, if appropriate.

8.2.3. Electrocardiograms

Screening: a single 12-lead ECG will be conducted per the Investigator's usual practice

Baseline: A single 12-lead ECG will be performed to ensure the participant's eligibility for the study (Section 5.2). Inpatient telemetry monitoring will be utilized per the unit's usual practice until the participant is discharged from the inpatient setting, but routine telemetry readings will not be collected as study data unless they pertain to a relevant AE.

48 hours post-TPIP administration follow-up: a single 12-lead ECG will be conducted per the Investigator's usual practice.

8.2.4. Clinical Safety Laboratory Assessments

See Section 10.2 (Table 7) for the list of clinical laboratory tests to be performed and the SoA (Table 1, Table 2, Table 5, Table 6) for the timing and frequency. All clinical laboratory tests will be performed locally by the study site.

The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the Investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 7 days after TPIP dosing must be repeated at the Investigator's discretion, consistent with the participant's level of disease until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

- If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology must be identified, and Insmed notified.]
- All protocol-required laboratory tests, as defined in Section 10, Appendix 2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.4).
- If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose modification), then the results must be recorded.

8.2.5. Pregnancy Testing

8.2.5.1. Single-dose Period

Willingness of WOCBP to undergo serum or urine pregnancy testing is a study eligibility criterion. Pregnancy tests will be conducted at screening, baseline, and Study Day 30. WOCBP

participants will be provided a home pregnancy test kit with instructions to conduct and report test results at the Study Day 30 follow-up visit which is scheduled to be by telephone call or telemedicine. If the participant elects to enter the optional EUT period and the remote safety follow-up visit overlaps with the start of the EUT period, the results of a urine pregnancy test will be recorded at the first visit in the extended treatment period.

8.2.5.2. Optional Extended Use Treatment Period

Urine pregnancy tests will be performed in-clinic at EUT Baseline (EUT Day 1) in WOCBP. WOCBP participants will be provided home pregnancy test kits with instructions to conduct the pregnancy tests every 30 days or more if required during the treatment and follow-up periods. Study site personnel will contact the participant every 30 days by telephone and record the pregnancy test results. An additional on-site urine test must be performed prior to starting any procedure that requires the use of ionizing radiation.

8.3. Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

The definitions of AEs and SAEs can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative). AEs may be solicited or unsolicited. Solicited and unsolicited AEs are defined in Section 10.3.

The Investigator is responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE as provided in the protocol and remain responsible for following up all AEs.

The Investigator should proactively follow participants with AEs until the EOS for each participant. At the EOS visit, the Investigator will record the AE status (stable or not stable) in the electronic CRF.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs (serious and non-serious) for the core, single-dose period will be collected from the signing of the ICF until the Study Day 30 follow-up visit at the time points specified in the SoA (Table 1, Table 2). Medical occurrences that begin after obtaining informed consent but before TPIP administration will be recorded as Medical History/Current Medical Conditions, not as AEs.

SAEs that occur after signing the ICF but before study IMP starts must be recorded and reported as SAEs. Non-serious medical occurrences that begin after obtaining informed consent but before TPIP administration will be recorded as Medical History/Current Medical Conditions, not as AEs.

For participants who enroll in the EUT period, AEs for the period from the single-dose Study Day 30 follow-up until the enrollment in the EUT will be collected during participant's screening for the optional EUT period. All AEs and SAEs for participants who choose to enroll in the optional EUT period will be recorded at the time points specified in the SoA (Table 5, Table 6).

All SAEs will be recorded and reported to Insmed or designee immediately and under no circumstance must this exceed 24 hours, as indicated in Appendix 3, (Section 10.3). The Investigator will submit any updated SAE data to Insmed within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study IMP or study participation, the Investigator must promptly notify Insmed.

8.3.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. The Investigator should proactively follow participants with AEs until the EOS for each participant. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline due to study completion, then the site can report this information to the Medical Monitor by email or telephone.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to Insmed of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

Insmed has a legal responsibility to notify relevant health authorities and regulatory agencies about the safety of a study drug under clinical investigation. This study is being conducted in the USA only; regulatory requirements relating to safety reporting to the US FDA, IRBs, and investigators will be followed.

An Investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from Insmed will review and then file it along with other study documents and will notify the IRB, if appropriate according to local requirements.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Insmed policy and forwarded to Investigators as necessary. No serious adverse

reactions are considered expected for TPIP. Please refer to the Reference Safety Information in Section 6.1 of the Investigator's Brochure.

8.3.5. Pregnancy

Details of all pregnancies that occur in WOCBP participants within 30 days after TPIP administration will be collected. Male participants with WOCBP partners must continue to use contraception for 90 days after TPIP administration and report any pregnancies that occur within that time period.

If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to Insmed within 24 hours of learning of the pregnancy in a female participant or female partner of male participant and after obtaining the necessary signed informed consent from the female partner.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

Any female participant who becomes pregnant while participating in the study will be discontinued from the study.

8.3.6. Adverse Events of Special Interest (AESI)

There are no AESIs for TPIP that require special collection and rapid communication by the Investigator.

8.3.7. Medical Device Deficiencies

A medical device, the Plastiape capsule based Dry Powder Inhaler is being provided for use in this study to administer TPIP. To fulfill regulatory reporting obligations worldwide, the Investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a Medical Device deficiency and reporting requirements and procedures for device deficiencies and AEs/SAEs resulting from device deficiencies can be found in Section 10.6.

8.3.7.1. Time Period for Detecting Medical Device Deficiencies

- Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the Investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such a deficiency is considered reasonably related to a medical device provided for the study, the Investigator will promptly notify Insmed.

The method of documenting Medical Device Deficiency is provided in Section 10.6.

8.3.7.2. Follow-Up of Medical Device Deficiencies

Follow-up applies to all participants who experienced a device deficiency.

The Investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.

New or updated information will be recorded on the originally completed form with all changes signed and dated by the Investigator.

8.3.7.3. Prompt Reporting of Device Deficiencies to Insmed

Device deficiencies will be reported to Insmed within 24 hours after the Investigator determines that the event meets the protocol definition of a medical device deficiency.

8.3.7.4. Regulatory Reporting Requirements for Device Deficiencies

The Investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for Insmed to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The Investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB.

8.4. Pharmacokinetic Assessments

The schedule for PK assessments and sampling windows during the single-dose period is shown in Table 3. The 48 (± 4) hour post-TPIP administration blood draw is expected to be done on an outpatient basis.

8.4.1. PK Sample Collection

Plasma blood samples of approximately 10 mL each will be collected for measurement of plasma concentrations of TP and TRE as specified in the SoA (Section 1.4).

A maximum of 2 samples may be collected at additional time points during the study if an SAE occurs or at early termination.

Each PK plasma sample will be divided into 2 aliquots (1 each for PK analysis and the other for backup. All samples will be stored frozen (-70°C or -20°C) until shipment and then stored at -70°C until analysis. The actual date and time (24-hour clock time) of each sample will be recorded.

Full instructions for the collection and handling of PK samples will be provided by Insmed in a separate Laboratory Manual.

8.4.2. PK Analysis

Individual PK parameters of TRE and TP will be determined using non-compartmental analysis for the following parameters: C_{max}, t_{max}, $AUC_{t1–t2}$, $AUC_{0–\infty}$, CL/F, Vd/F, and $t_{1/2}$.

8.4.3. Pharmacokinetic and Pharmacodynamic Evaluations

Relationships between PK (TP dose and TRE exposure) and PD effects and safety will be explored and reported separately.

8.5. Genetics / Pharmacogenomics

Genetic and/or pharmacogenomic analyses are not included in this study.

8.6. Biomarkers

A blood sample for NT-pro-BNP will be taken at screening if needed as part of study inclusion criteria (Section 5.1).

Blood samples (5-7 mL per time point) will be collected for biomarker measurement at Baseline and at 4 and 8 hours after TPIP administration. The plasma generated from the blood samples will be stored frozen (-70 C or lower is preferred) until shipment and analysis.

Full instructions for the collection and handling of biomarker samples will be provided by Insmed in a separate Laboratory Manual.

8.7. Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

8.8. Immunogenicity Assessments

Immunogenicity assessments do not apply to this study of a small molecule.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

No statistical hypotheses will be evaluated in this study.

9.2. Sample Size Determination

The sample size for this study is not based on statistical power calculations. The planned number of evaluable participants to complete the study is approximately 6-10.

9.3. Analysis Sets

The analysis sets comprise participants who are considered evaluable for the parameters under consideration.

All participants who receive a single dose of TPIP will be considered evaluable for safety and included in the safety population.

All participants who receive a single dose of TPIP and have a least one measurable post-dose plasma TP/TRE concentration will be considered evaluable for PK and included in the PK population.

All participants who receive a single dose of TPIP and have a Baseline datapoint and at least one measurable post-dose PD datapoint will be considered evaluable for PD and included in the PD population.

All participants who receive a single dose of TPIP and have at least 1 measurable post-dose biomarker datapoint will be considered evaluable for biomarkers and included in the biomarker population.

9.4. Statistical Analyses

The statistical analysis plan will be finalized prior to Database Lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

There is no hypothesis-testing in this study and no inferential statistical analyses will be conducted. There will be no proxy values for missing data. Participant PK, PD, and biomarker data will be presented individually in listings and graphs as appropriate for each variable.

The frequency of TEAEs is the primary endpoint for this study. All safety analyses will be performed on the safety population. AE listings as required by ICH E3 guidelines will be produced. TEAEs, SAEs, AEs leading to treatment and/or study withdrawal, and AESIs will be listed for each participant along with outcome, severity, and relatedness to study IMP. Ad hoc summaries of TEAEs may be prepared if the volume of data allow.

PK and PD values for secondary endpoints will be listed and graphed if appropriate for each evaluable participant.

PK and PD values for exploratory endpoints will be listed and graphed as appropriate for each participant.

9.4.2. ECG, Vital Signs, Clinical Laboratory Values

ECG data will be listed for each participant. Vital signs data that are not considered part of a PD assessment (Section 8.1) will be listed for each participant. Clinical laboratory values will be listed for each participant.

9.5. Interim Analysis

All available safety, PK, and PD data from each participant will be evaluated by the SRC prior to the next participant in order to determine the value of proceeding with the study and the TPIP dose for each subsequent participant (Section 4.3).

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

a. Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
b. Applicable ICH Good Clinical Practice (GCP) Guidelines
c. Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, Instructions for Use of the Plastiape capsule based Dry Powder Inhaler, and other relevant documents must be submitted to an IRB by the Investigator and reviewed and approved by the IRB before the study is initiated.

Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

d. Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
e. Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures
f. Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB, and all other applicable local regulations

10.1.2. Protocol Deviations

The Investigator must conduct the study in compliance with the protocol as agreed to by Insmed and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRB.

The Investigator must notify the IRB of deviations from the protocol in accordance with IRB reporting requirements.

As of May 2020, due to concern regarding COVID-19, there may be restrictions to participant attendance at in-clinic visits or elective inpatient admissions. In the event participants are restricted to attend in-clinic visits, or if the participant has concern regarding travel and attending in-clinic visits (due to potential public health concerns), the site must contact Insmed on how to

conduct the scheduled assessments, and decisions must be documented in the source documentation. Where necessary, in-clinic visits may be conducted via telemedicine link and home health care visits.

10.1.3. Public Health Emergency Situations

During the COVID-19 public health emergency, Insmed, IRBs, and Investigators shall follow the most current version of local guidance to assure the safety of study participants, maintain compliance with GCP, and minimize risks to study integrity. The continuity of clinical study conduct and oversight may require implementation of temporary or alternative mechanisms, which will remain in effect only for the duration of the local public health emergency. Examples of such mechanisms may include, but are not limited to, any of the following: telephone contact, virtual visits, telemedicine visits, online meetings, non-invasive remote monitoring devices, use of local clinic or laboratory locations, and home visits by skilled staff. The site must contact Insmed on how and when to implement temporary and/or alternative mechanism of scheduled assessments, and all decisions taken must be documented in the source documentation. Additionally, all temporary mechanisms utilized, and the resulting deviations from planned study procedures are to be documented as being related to COVID-19.

In a situation where local health authorities declare a public health emergency while the study is ongoing, the suggested guidance in the following subsections must be followed.

10.1.3.1. Continuation or Suspension of the Study

Ensuring the safety of trial participants is paramount. Insmed (Insmed Incorporated), in consultation with clinical Investigators and IRB, will determine if the protection of a participant's safety, welfare, and rights are best served by continuing or stopping the trial at the specific site. Such decision will depend on specific circumstances, including the ability to conduct appropriate safety monitoring, the potential impact on the investigational product supply chain, and other considerations.

If the decision is to continue the study, the following considerations will be taken into account:

10.1.3.1.1. Study Recruitment

Insmed will communicate to the sites the decision on whether to continue or suspend recruitment after considering the specific circumstances of each site, recommendation by the IRB, and its local health authority mandates. If, due to COVID-19, study discontinuation exceeds the assumed rate, Insmed may allow enrollment past the assumed sample size.

10.1.3.1.2. Participants Already Enrolled in the Study

If the decision is to continue the participation of participants already enrolled, the following steps must be taken:

- If a participant is not able to complete a protocol specified study visit, it may be necessary to adjust the visit schedule, convert in-clinic visits to telemedicine visits, and/or postpone study procedures until the next available in-clinic study visit. If there is information available from previous visits (e.g., laboratory assessments) that

requires follow-up procedures or other safety assessments, the Investigator will decide if an on-site visit or home healthcare visit is required or whether the participant's safety can be preserved by other means.

10.1.3.1.3. Participants Infected by COVID-19

If a participant has had a past documented mild to moderate COVID-19 infection prior to enrollment in the trial but the participant has recovered and the current diagnostic tests are negative (negative antigen by any diagnostic laboratory kit), the participant can be screened, at the Investigator's discretion. Participants who experienced hospitalization, severe disease, and/or COVID-19 acute respiratory distress syndrome (ARDS) must be excluded.

If a participant has a documented infection by COVID-19 while in the trial, the event will be reported as an AE or SAE, depending on the criteria. The Investigator will follow the guidance provided by health authorities in the treatment of those participants.

10.1.4. Financial Disclosure

The disclosed financial interest of the Investigator/sub-investigator must be collected before screening of the first participant, following study completion at the Investigator site and 1 year following overall study completion. The Investigator/sub-investigator must promptly update this information if any relevant changes occur during this period.

10.1.5. Informed Consent Process

Before a participant's participation in the study, it is the Investigator's responsibility to obtain freely given consent, in writing, from the participant or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any study IMPs are administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective participant, to the participant's participation in the clinical study. An informed consent document that includes both information about the study and the consent form will be prepared and given to the participant. This document will contain all the elements required by the ICH E6 (R2) Guideline for GCP and any additional elements required by local regulations. The written ICF must be prepared in the local language(s) of the potential participant population.

In obtaining and documenting informed consent, the Investigator must comply with the applicable regulatory requirements, and must adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form and any revision(s) must be approved by the IRB prior to being provided to potential participants.

The participant's written informed consent (written or electronic) must be obtained prior to his/her participation in the study, and must be documented in the participant's medical records, as required by applicable regulations. The ICF must be signed and personally dated by the participant or a legally acceptable representative, and by the person who conducted the informed consent discussion (not necessarily the Investigator). The signed ICF must be retained in accordance with institutional policy, and a copy of the signed consent form must be provided to

the participant or legal representative. The date and time that informed consent was given must be recorded in the CRF.
Participants who are rescreened are required to sign a new ICF.

10.1.6. Protection of Participant Identification and Confidentiality

The Investigators and Insmed will preserve the confidentiality of all participants taking part in the study, in accordance with GCP and local regulations.

The Investigator must ensure that the participant's anonymity is maintained. On the CRF or other documents submitted to Insmed, participants must be identified by a unique participant identifier as designated by Insmed. Documents that are not for submission to Insmed (e.g., signed ICFs) must be kept in strict confidence by the Investigator.

In compliance with ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB direct access to review the participant's original medical records for verification of study-related procedures and data. The Investigator is obligated to inform the participant that his/her study-related records will be reviewed by the above-named representatives without violating the confidentiality of the participant.

Participant names will not be supplied to Insmed. A participant number will be recorded in the CRF, and if the participant name appears on any other document (e.g., laboratory report), it must be obliterated on the copy of the document to be supplied to Insmed. All records will be kept confidential to the extent provided by federal, state, and local laws. The participants will be informed that representatives of Insmed, IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

The Investigator will maintain a personal participant identification list (participant numbers with the corresponding participant names) to enable records to be identified.

10.1.7. Committee Structure

An SRC will be responsible for monitoring safety data. The SRC will comprise all Investigators and key members of the Insmed Study Team (including but not limited to Medical Monitor, Medical Director(s), Safety/Pharmacovigilance Physician, Statistician, Clinical Pharmacologist) and external expert consultants. The SRC will continuously monitor all available safety, PD and PK data for each participant and will obtain consensus regarding the safety of continuing the study, the next TPIP dose, and clinical care of the next participant. Expert consultants may be invited to review and interpret participant data. With any safety findings, a decision will be made, based on the review, as to whether enrollment in the study will be allowed to continue. Decisions regarding final database values for PD parameters may be adjudicated by the SRC.

10.1.8. Dissemination of Clinical Study Data

Insmed will provide study information for inclusion in national registries according to national/local regulatory requirements.

Results of this study will be disclosed according to the relevant national regulatory requirements.

10.1.9. Data Quality Assurance

The Investigator/investigational site will permit study-related monitoring, audits, IRB review and regulatory inspections by providing direct access to source data/documents. Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of a clinical study.

10.1.9.1. Data Collection

All data obtained for this study will be entered into a 21 CFR Part 11 compliant Data Management System provided by Insmed or its designee. These data will be recorded with an EDC system using CRFs. The Investigator will ensure the accuracy and completeness of the data reported to Insmed. All data entry, modification or deletion will be recorded automatically in an electronic audit trail.

The Investigator will provide access to his/her original records to permit a representative from Insmed to verify the proper transcription of data. Data reported in the CRFs must be consistent with and substantiated by the participant's medical record and original source documents. The CRF data will be monitored by Insmed or designee. The final, completed CRF Casebook for each participant must be electronically signed and dated by the PI within the EDC system to signify that the Investigator has reviewed the CRF and certifies it to be complete and accurate.

Insmed will retain the final CRF data and audit trail. A copy of all completed CRFs will be provided to the Investigator.

10.1.9.2. Study Monitoring

Before study initiation, at a site initiation visit or at an Investigator's meeting, an Insmed representative will review the protocol, CRF, Investigator Brochure, and any study-related materials with the Investigators and their staff. During the study, Insmed study monitor or its designee will visit the site regularly to check the completeness of participant records, the accuracy of entries on the CRFs, adherence to the protocol, adherence to ICH GCP and applicable regulatory requirements, the progress of enrollment, and also to ensure that study IMP is being stored, dispensed, and accounted for according to specifications.

The Investigator must give the monitor access to relevant hospital or clinical records to confirm their consistency with the CRF entries. Participant confidentiality will be maintained by the study center. Insmed monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of primary activity and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study specific monitoring plan.

10.1.9.3. Audits and Inspections

Domestic and foreign regulatory authorities, the IRB, and an auditor authorized by Insmed may request access to all source documents, CRFs, and other study documentation for onsite audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must

provide support at all times for these activities. Medical records and other study documents may be copied during audit or inspection provided that participant names are obliterated on the copies to ensure confidentiality.

If an inspection is requested by a regulatory authority, the Investigator will inform Insmed, immediately that this request has been made.

10.1.9.4. Study Record Retention

Study documents must be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents must be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of Insmed. It is the responsibility of Insmed to inform the Investigator when these documents no longer need to be retained.

10.1.9.5. Source Documents

Source documentation is the point of initial recording of a piece of data. Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.10. Study Files and Materials

Before the start of any study related procedures, all initial documents required by ICH GCP, Good Pharmacoepidemiology Practice, and applicable local regulations must be available in the relevant files maintained by Insmed (or delegate) and the Investigator. An Investigator Study File prepared by Insmed (or delegate), containing all applicable documents for use at the study site, will be made available to the Investigator before the start of the study. A list of personnel and organizations responsible for conduct of the study as well as the list of Investigator-delegates (e.g., sub-investigator) at each site will be included in the Investigator Study File. The respective files will be kept and updated by Insmed (or delegate) and the Investigator, as applicable.

All study documentation and materials maintained in the Investigator Study File at the study site must be available for inspection by Insmed's study monitor (or delegate) to determine that all required documentation is present and correct.

The study may be audited by qualified delegates from Insmed or a competent regulatory authority.

10.1.11. Use of Stored Samples and Data

Stored samples will be labeled with study and participant information and secured with limited access and retained per protocol requirements and in accordance with the laboratory's operating procedures. Electronic data will be kept in password protected computers at the laboratory and then transferred to Insmed or CRO, as applicable, for data analysis. Samples and corresponding data will be tracked using the laboratory's specimen tracking system.

Prior Insmed and IRB approval are required before using or sharing study samples or data in ways not specifically specified in the study protocol during conduct of this study.

Any loss or unanticipated destruction of samples (e.g., freezer malfunction) or data (e.g., loss of a data sheet with individually identifiable information) that violates or compromises the scientific integrity of study data must be reported to Insmed and the IRB.

At any time, participants may inform the Investigator in writing that they do not wish to have their samples stored beyond the completion (termination) of the study. In this case, the Investigator will request that all known remaining samples be destroyed and report the disposition of samples to the requesting participants and the IRB.

10.1.12. Disposition of Stored Samples and Data

Participant samples will be secured with limited access and retained per protocol requirements and in accordance with the laboratory's operating procedures. Samples stored by the central laboratories will be labeled with the participant's study identification information. Data will be kept in password protected computers at the laboratory and then transferred to the vendor for data analysis. Samples and corresponding data acquired will be tracked using the laboratory's specimen tracking system.

In the future, if other Investigators may wish to study these samples and/or data, they need to obtain Insmed approval and participant consent before any sharing of samples and/or data.

Any loss or unanticipated destruction of samples (e.g., due to freezer malfunction) or data (e.g., loss of a data sheet with individually identifiable information) that results in a violation that compromises the scientific integrity of the data collected for the study will be reported to Insmed and the IRB.

Additionally, participants may withdraw authorization in writing to decline their sample storage for a period of up to 2 years beyond the duration of the study. In this case, the PI will request the destruction of all known remaining samples and report what was done to both the participant and to the IRB. This decision will not affect the individual's participation in the study.

10.1.13. Study and Site Start and Closure

Before the start of the study at each study site, Insmed's study monitor (or delegate) shall confirm adequacy of the facilities by study site visit or other acceptable methods.

The Investigator may not enroll any participant into the study before Insmed has received written approval or a favorable opinion from the IRB for conducting the study and a formal meeting has been conducted by Insmed's study monitor (or delegate) to initiate the study. This meeting will include a detailed review of the study plan, and completion of the CRF.

10.1.13.1. First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants. The first participant screened for participation in the study is considered the first act of recruitment.

10.1.13.2. Study/Site Termination

Insmed or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of Insmed. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.
The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.
Reasons for the early closure of a study site by Insmed or Investigator may include but are not limited to:
For study termination:

- Discontinuation of further study IMP development

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB or local health authorities, Insmed's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, Insmed shall promptly inform the Investigators, the IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and must assure appropriate participant therapy and/or follow-up.

10.1.14. Protocol Amendments

Any substantial change or addition to this protocol requires a written protocol amendment that must be approved by Insmed, before implementation. Amendments significantly affecting the safety of participants, the scope of the investigation, or the scientific quality of the study, require additional approval by the applicable regulatory authority(ies) and IRBs. Copies of the applicable written approvals must be filed in Insmed files and investigator site files.

The requirements for approval must in no way prevent any immediate action from being taken by the Investigator or by Insmed in the interests of preserving the safety of all participants included in the study. If an immediate change to the protocol is felt to be necessary by the Investigator and is implemented by him/her for safety reasons, Insmed or its agent must be notified and the applicable regulatory authority(ies)/IRBs must be informed as soon as possible. Any other regional reporting requirements must be adhered to.

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or regulatory authority/IRB approval, but the regulatory authority(ies)/IRBs must be kept informed of such administrative changes in accordance with country specific requirements.

10.1.15. Financing and Insurance

10.1.15.1. Finances

Prior to starting the study, the Investigator and/or institution will sign a clinical study agreement with Insmed. This agreement will include the financial information agreed upon by the parties.

10.1.15.2. Reimbursement, Indemnity, and Insurance

Reimbursement, indemnity, and insurance shall be addressed in a separate agreement on terms agreed upon by the parties.

10.1.15.3. Participant Reimbursement, Liability and Insurance

The civil liability of the involved parties with respect to financial loss due to personal injury and other damage that may arise as a result of this study being conducted are governed by the applicable legal requirement(s).

Insmed will provide insurance to the Investigator if required by the applicable regulatory and legal requirement(s).

If required by local law, participants taking part in this study will be insured against any injury caused by the study in accordance with the applicable regulatory and legal requirement(s).

10.1.16. Publication Policy

Any formal presentation or publication of data collected from this study will be considered as a joint publication by the Investigator(s) and the appropriate personnel of Insmed. Authorship will be determined by mutual agreement. For multi-center studies, it is mandatory that the first publication be based on data from all centers, analyzed as stipulated in the protocol by Insmed and statisticians, and not by the Investigators themselves. Investigators participating in multi center studies agree not to present data gathered from a single center or a small group of centers before the full, initial publication, unless formally agreed to by all other Investigators and Insmed.

Insmed must receive copies of any intended communication in advance of publication (at least 15 working days for an abstract or oral presentation and 45 working days for a journal

submission). Insmed will review the communications for accuracy (thus avoiding potential discrepancies with submissions to regulatory authorities), verify that confidential information is not being inadvertently divulged, and to provide any relevant supplementary information. Authorship of communications arising from pooled data may include members from each of the contributing centers as well as Insmed personnel.

At the conclusion of the study, after the data are analyzed, the results of study will be reported in a clinical study report.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 7 will be performed by the local laboratory. If local laboratory results are used to make a study IMP decision or response evaluation, the results must be recorded. Protocol-specific clinical laboratory requirements for the inclusion or exclusion of participants are detailed in Section 5.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 7: Protocol-Required Safety Laboratory Tests, INS1009-201

Category	Laboratory Parameters
Clinical Chemistry	Sodium, chloride, potassium, CO_2, magnesium, calcium, glucose, phosphate, total bilirubin (with direct and indirect fractionation, if total bilirubin is elevated >2 ULN), alkaline phosphatase, LDH, AST, ALT, CPK, albumin, total protein, creatinine, urea-nitrogen, uric acid, estimated glomerular filtration rate
Hematology	Hemoglobin, erythrocytes, hematocrit, MCH, MCV, MCHC, leukocytes, differential blood count of neutrophils, eosinophils, basophils, monocytes, lymphocytes, and platelets
Coagulation[a]	PT, PTT, INR
Serology[a]	HIV antibody, hepatitis B surface antigen [HBsAg], Hepatitis C virus antibody
Pregnancy test	Highly sensitive serum or urine hCG

[a] Not included in EUT screening for participants enrolling in the extended use treatment period.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; CO_2 = carbon dioxide; CPK = creatine phosphokinase; hCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; INR = international normalized ratio; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PT = prothrombin time; PTT = partial thromboplastin time; ULN = upper limit of normal

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

The definitions and procedures in this Appendix (Appendix 3) are for AEs and SAEs that do not involve the Plastiape capsule based Dry Powder Inhaler. For reporting device deficiencies or AEs involving the Plastiape capsule based Dry Powder Inhaler, please see Section 10.6.

10.3.1. Definition of AE

AE Definition
An AE is defined as any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, October 1994). A treatment emergent adverse event (TEAE) is defined as any AE that occurs after the first dose of study IMP and within 28 days after the last dose of study IMP

Events Meeting the AE Definition
Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), that worsen from Baseline, are considered clinically significant in the medical and scientific judgment of the Investigator (e.g., not related to progression of underlying disease), that are associated with signs and/or symptoms, require therapeutic intervention, or lead to discontinuation of the administration of study IMP must be reported as an AE Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. New conditions detected or diagnosed after study IMP administration even though it may have been present before the start of the study. Signs, symptoms, or the clinical sequelae of a suspected IMP- IMP interaction. Signs, symptoms, or the clinical sequelae of a suspected overdose of either study IMP or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses must be reported regardless of sequelae. The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. “Lack of efficacy” or “failure of expected pharmacological action” also constitutes an AE or SAE. Lack of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the PK and PD assessments.

Events <u>NOT</u> Meeting the AE Definition

Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Study INS1009-201 requires an overnight inpatient treatment period (Study Days 1-2). Complications that occur during the inpatient treatment period are AEs. If a complication prolongs the planned hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE must be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Is a suspected transmission of any infectious agent via an authorized medicinal product
g. Is an important medical event
h. Other situations:

Medical or scientific judgment must be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events must usually be considered serious.

g. Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of IMP dependency or IMP abuse.

10.3.3. Recording and Follow-up of AE and/or SAE

AE and SAE Recording

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The Investigator will then record all relevant AE/SAE information.

It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to Insmed in lieu of completion of the completed AE reporting form.

There may be instances when copies of medical records for certain cases are requested by Insmed. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Insmed.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities.

Severe: An event that prevents normal everyday activities. An AE that is assessed as severe must not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

The Investigator is obligated to assess the relationship between study IMP and each occurrence of each AE/SAE.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study IMP administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to Insmed. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Insmed.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Insmed to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide Insmed with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to Insmed within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

All SAEs, regardless of causality, must be reported to the organization delegated by Insmed on a Serious Adverse Event Report Form within 24 hours of becoming aware of the event; corrections and additions are required to be submitted within 24 hours. Study-specific email, phone, and fax number for SAE reporting information will be provided to the study sites.

Unexpected drug related SAEs as assessed by Insmed or authorized person qualify for expedited reporting and will be reported to the IRB, regulatory authorities, participating Investigators and, if cross reporting is required for SUSARs, in accordance with all applicable global laws and regulations. A SUSAR is a Serious Adverse Reaction, which is suspected to be caused by the investigational medicinal product and which is unexpected; e.g., its nature or severity is not

consistent with the information in the relevant Reference Safety Information. SAEs, including those that do not meet requirements for expedited reporting, and all other AEs will be reported to the regulatory agencies as appropriate (e.g., for the FDA these are reported in the Investigational New Drug annual report and for the European Medicines Agency, these are reported in the Development Safety Update Report).

SAE Reporting to Insmed via an Electronic Data Collection Tool
The primary mechanism for reporting an SAE to Insmed will be the electronic data collection tool. If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours. The site will enter the SAE data into the electronic system as soon as it becomes available. After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Medical Monitor by email or telephone.

SAE Reporting to Insmed via Paper Data Collection Tool
Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to Insmed. In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting time frames.

10.4. Appendix 4: Contraceptive and Barrier Guidance

Contraceptive use by men and women of childbearing potential (WOCBP) must be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Highly effective contraception methods include true abstinence (refraining from heterosexual intercourse during the study); combined (estrogen and progestogen containing) or progestogen only hormonal contraception associated with inhibition of ovulation and supplemented with a double barrier (preferably male condom); intrauterine devices; intrauterine hormone-releasing systems; or vasectomized partner.

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

INTRODUCTION

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a participant meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with Insmed clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug-Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

DEFINITIONS

Potential Hy's Law (PHL)

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3×ULN and total bilirubin (TBL) ≥2×ULN at any point during the study irrespective of an increase in alkaline phosphatase (ALP). The elevations do not have to occur at the same time or within a specified time frame.

Hy's Law (HL)

AST or ALT ≥3× ULN and TBL ≥2×ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug. The elevations do not have to occur at the same time or within a specified time frame.

IDENTIFICATION OF POTENTIAL HY'S LAW CASES

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

1. ALT ≥ 3xULN
2. AST ≥ 3xULN
3. TBL ≥ 2xULN

The Investigator will review without delay each new laboratory report and if the identification criteria are met will:

1. Notify Insmed representative
2. Determine whether the participant meets PHL criteria (see DEFINITIONS of this Appendix) by reviewing laboratory reports from all previous visits

3. Promptly enter the laboratory data into the laboratory CRF

FOLLOW-UP

POTENTIAL HY'S LAW CRITERIA NOT MET

1. If the participant does not meet PHL criteria the Investigator will:
2. Inform Insmed representative that the participant has not met PHL criteria.
3. Perform follow-up on subsequent laboratory results according to the guidance provided in the clinical study protocol

POTENTIAL HY'S LAW CRITERIA MET

If the participant does meet PHL criteria the Investigator will:

- Notify Insmed representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or Baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician
- Complete the 3 Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

The instructions in this section must be followed for all cases where PHL criteria were met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than drug-induced liver injury caused by the IMP. The Insmed Medical Science Director and Global Safety Physician will also be involved in this review together with other participant matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

- If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE
- If the alternative explanation is not an AE, record the alternative explanation on the appropriate CRF

If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow Insmed standard processes.

If it is agreed that there is no explanation that would explain the ALT or AST and TBL elevations other than the IMP:

•Report an SAE (report term ‘Hy’s Law’) according to Insmed standard processes.

- The ‘Medically Important’ serious criterion must be used if no other serious criteria apply
- As there is no alternative explanation for the HL case, a causality assessment of ‘related’ must be assigned.

If there is an unavoidable delay, of over 3 weeks in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term ‘Potential Hy’s Law’) applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

10.6. Appendix 6 Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

The definitions and procedures detailed in this appendix are in accordance with ISO 14155.

Both the Investigator and Insmed will comply with all local reporting requirements for medical devices.

The detection and documentation procedures described in this protocol apply to all Insmed medical devices provided for use in the study. See Section 6.1.3 for the list of Insmed medical devices.

10.6.1. Definition of Medical Device AE and ADE

Medical Device AE and ADE Definition
An AE is any untoward medical occurrence in a clinical study participant, users, or other persons, temporally associated with the use of study IMP, whether or not considered related to the investigational medical device. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved. An adverse device effect (ADE) is defined as an AE related to the use of an investigational medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.6.2. Definition of Medical Device SAE, SADE and USADE

A Medical Device SAE is an any serious adverse event that:
a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in: A life-threatening illness or injury. The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death if it were more severe. A permanent impairment of a body structure or a body function. Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function. Chronic disease (MDR 2017/745).
c. Led to fetal distress, fetal death, or a congenital abnormality or birth defect

d. Is a suspected transmission of any infectious agent via a medicinal product
SADE definition
A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of an SAE. Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.
Unanticipated SADE (USADE) definition
An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is defined as a serious adverse device effect that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report (Section 2.3).

10.6.3. Definition of Device Deficiency

Device Deficiency Definition
A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and information supplied by the manufacturer.

10.6.4. Recording and Follow-up of AE and/or SAE and Device Deficiencies

AE, SAE, and Device Deficiency Recording
When an AE/SAE/device deficiency occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. The Investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the Investigator's normal clinical practice and on the appropriate form. It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to Insmed in lieu of completion of the AE/SAE/device deficiency form. There may be instances when copies of medical records for certain cases are requested by Insmed. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Insmed. The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. For device deficiencies, it is very important that the Investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency. A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE/SAE/device deficiency reported during the study and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe must not be confused with an SAE. "Severe" is a category used for rating the intensity of an event; both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, **not** when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study IMP and each occurrence of each AE/SAE/device deficiency.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship, cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study IMP administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure and/or Instructions for Use of the device in his/her assessment.
- For each AE/SAE/device deficiency, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/device deficiency and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to Insmed. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Insmed.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE/SAE/device deficiency

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Insmed to elucidate the nature and/or causality of the AE/SAE/device deficiency as fully as

possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide Insmed with a copy of any post-mortem findings including histopathology.
New or updated information will be recorded in the originally completed form.
The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.6.5. Reporting of SAEs

SAE Reporting to Insmed via an Electronic Data Collection Tool

The primary mechanism for reporting an SAE to Insmed will be the electronic data collection tool.
If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next table) to report the event within 24 hours.
The site will enter the SAE data into the electronic system as soon as it becomes available.
After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next table) or to the Medical Monitor by telephone.

SAE Reporting to Insmed via Paper Data Collection Tool

Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to Insmed.
In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE paper data collection tool sent by overnight mail or courier service.
Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE paper data collection tool within the designated reporting time frames.

10.6.6. Reporting of SADEs

SADE Reporting to Insmed

NOTE: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

Any device deficiency that is associated with an SAE must be reported to Insmed within 24 hours after the Investigator determines that the event meets the definition of a device deficiency.

Insmed will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs as required by national regulations.

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Signature Page for Study INS1009-201 Protocol - Original

Approve	[redacted] 02-Nov-2020 18:55:52 GMT+0000

CLINICAL STUDY PROTOCOL

An Open-Label Single Dose Study to Assess the Safety, Pharmacokinetics, and Pharmacodynamics of Treprostinil Palmitil Inhalation Powder in Participants with Pulmonary Arterial Hypertension

Protocol Number: INS1009-201

Version Number: 1

Amendment Number: Not Applicable

Compound: Treprostinil Palmitil Inhalation Powder (TPIP)

Study Phase: 2a

Insmed Name: Insmed Incorporated

Legal Registered Address:
700 US Highway 202/206
Bridgewater, NJ 08807-1704
USA

Regulatory Agency Identifier Number(s)
IND: 147264

Date: 02 NOV 2020

IMPORTANT CONTACTS

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ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ALT	alanine amino transferase
AST	aspartate amino transferase
AUC	area under the concentration-time curve
$AUC_{0-\infty}$	area under the concentration-time curve from time zero to infinity
AUC_{t1-t2}	area under the plasma concentration-time curve from time zero to time of last measurable concentration
CL/F	apparent total clearance of drug from plasma after extravascular administration
C_{max}	maximum (peak) plasma concentration of the drug
CO	cardiac output
CRF	case report form
CRO	contract research organization
CT	computerized tomography
DILI	drug induced liver injury
DPI	dry powder inhalation
ECG	electrocardiogram
EDC	electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
HL	Hy's Law
ICF	informed consent form

ICH	International Council for Harmonisation
ICU	intensive care unit
IMP	investigational medicinal product
IRB	investigational review board
IV	intravenous
MAD	multiple ascending dose
MVO_2	mixed venous oxygen saturation
NT-pro-BNP	N-terminal (NT)-pro hormone brain natriuretic peptide
PAH	pulmonary arterial hypertension
PAP	pulmonary arterial pressure
PD	pharmacodynamic(s)
PH	pulmonary hypertension
PHL	potential Hy's Law
PI	principal investigator
PK	pharmacokinetic(s)
PVR	pulmonary vascular resistance
QID	four times daily
RAP	right atrial pressure
RHC	right heart catheter
RVP	right ventricular pressure
SAD	single ascending dose
SAE	serious adverse event
SARS CoV 2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous

SoA	schedule of activities/assessments
SUSAR	suspected unexpected serious adverse reaction
SRC	Safety Review Committee
$t_{1/2}$	elimination half-life
TBL	total bilirubin
TAPSE	tricuspid annular plane systolic excursion
TEAE	treatment emergent adverse event
t_{max}	time to maximum (peak) plasma concentration following drug administration
TPIP	treprostinil palmitil inhalation powder
TPIS	treprostinil palmitil inhalation suspension
TRE	treprostinil
TP	treprostinil palmitil
TVR	tricuspid valve regurgitation
ULN	upper limit of normal
US	United States
VCO_2	carbon dioxide production
Vd/F	apparent volume of distribution at terminal phase
WHO	World Health Organization
WOCBP	woman of child-bearing potential

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

An Open-Label Single Dose Study to Assess the Safety, Pharmacokinetics and Pharmacodynamics of Treprostinil Palmitil Inhalation Powder in Participants With Pulmonary Arterial Hypertension

Rationale:

Treprostinil palmitil (TP) is an inactive prodrug of treprostinil (TRE), which is widely used in the treatment of pulmonary hypertension (PH). Treprostinil palmitil inhalation powder (TPIP) is a dry powder for inhalation formulation of TP. TPIP is being developed for the treatment of pulmonary arterial hypertension (PAH; World Health Organization (WHO) Group 1 PH). TPIP is expected to provide extended release of TRE in the lung with the goals of less frequent and more convenient and consistent dosing while reducing the frequency and severity of dose-limiting side effects associated with the currently approved forms of TRE. No studies of TP or TPIP have been conducted in patients with PAH. The purpose of this study is to evaluate the safety, pharmacokinetics (PK), and pharmacodynamic (PD) effects of a single dose of TPIP in patients with PAH.

The starting and planned doses for this study are primarily based on the safety and tolerability of treprostinil palmitil inhalation suspension (TPIS) in healthy participants following single inhalation at 85 to 340 µg (Study INS1009-101). In this study, the systemic exposure for TRE at 340 µg was low (AUC < 2.5 ng*h/mL) with an elimination $t_{1/2}$ of approximately 7 hours. In rats, the PK profile of TP inhalation solution was similar to that of TP inhalation powder. Preliminary, dose-normalized concentration data from a Phase 1 study of TPIP in healthy participants (INS1009-102) suggests a similar bioavailability in humans between TPIP and TPIS.

Objectives and Endpoints:

Objectives	Endpoints
Primary	Primary
• To evaluate the safety and tolerability of single doses of TPIP in participants with PAH	• Frequency of TEAEs
Secondary	Secondary
• To evaluate the PD effects of single doses of TPIP on PVR in participants with PAH over the first 24 hours following administration	• Change from Baseline in PVR at 8 and 24 hours after TPIP administration

• To evaluate the PK of TPIP as TRE in participants with PAH	• C_{max}, t_{max}, $AUC_{t1–t2}$, $AUC_{0–\infty}$, $t_{1/2}$ of TRE in plasma

TPIP=treprostinil palmitil inhalation powder; PAH=pulmonary arterial hypertension; TEAE=treatment emergent adverse event; PD=pharmacodynamic; PVR=pulmonary vascular resistance; PK=pharmacokinetics; TP=treprostinil palmitil; TRE=treprostinil; C_{max}=maximum observed concentration; t_{max}=time to maximum concentration after drug administration; $AUC_{t1–t2}$= area under the concentration time curve from time zero to last sampling timepoint with measurable concentration; $AUC_{0–\infty}$=area under the concentration time curve from time zero to infinity; $t_{1/2}$=elimination half-life

Overall Design:

This is a Phase 2a, open-label, nonrandomized single-dose study to assess the safety, tolerability, PD effects, and PK of TPIP administered to participants with PAH. This is the first study of TPIP in patients with PAH. Each participant will receive a single dose of TPIP, which may vary from participant to participant, as determined by the Safety Review Committee (SRC) for the study. The study includes a 24-hour inpatient observation period following TPIP dosing, during which PK, PD, and safety parameters will be assessed. The study is designed to ensure the safety of and maintain minimal risk to participants. The cardiopulmonary and overall functional status of patients with PAH can be labile and medical instability can develop quickly. As such, there is considerable flexibility built into the protocol to allow Investigator discretion with the frequency, timing, and/or conduct of PD and PK assessments to again ensure participants' safety.

Brief Summary:

The study is designed to investigate the safety and acute pharmacokinetic (PK) and pharmacodynamic (PD) effects of a single dose of trepostinil palmitil inhalation powder (TPIP) in participants with pulmonary arterial hypertension (PAH). Intensive monitoring of pulmonary vascular resistance, cardiac output, right ventricular pressure, pulmonary arterial pressure, hemoglobin, right atrial pressure, and mixed venous oxygen saturation via right heart catheter in an appropriate inpatient setting is essential to understand how TPIP affects cardiopulmonary hemodynamics and to elucidate dose- and PK-effect relationships. Some assessments and study activities (resting respiratory gas exchange assessment, transthoracic echocardiogram, pulmonary computerized tomography scan) for exploratory endpoints are optionally left to the discretion of the individual Investigator, based on participant safety and study site capabilities.

For individual participants, the study will consist of an outpatient screening period lasting up to 30 days. The inpatient treatment period will start on Study Day 1 and is expected to last overnight into Study Day 2. Outpatient PK sampling and safety follow-up at 36 and 48 hours post TPIP dose will extend into Study Day 3. A remote safety follow-up visit (telephone visit) is scheduled for Study Day 30 (± 2 days).

Number of Participants:

Approximately 6 to 10 evaluable participants are planned. Evaluable participants for safety are those who receive a single dose of TPIP; evaluable participants for PD and PK endpoints are those who receive a single dose of TPIP and have at least 1 post-TPIP administration PK or PD datapoint.

Treatment Groups and Duration:
This is a single-dose, open-label, non-randomized study. There are no predefined treatment groups. The dose determination for each participant will be made based on all available PK, PD, and safety data at the time of the participant's entry into the study

Safety Review Committee:
A Safety Review Committee (SRC) will be chartered. The SRC will comprise all Investigators and key members of the Insmed Study Team (including but not limited to Medical Monitor, Medical Director(s), Safety/Pharmacovigilance Physician, Statistician, Clinical Pharmacologist) and possible external expert consultants. The SRC will continuously monitor all available safety, PD and PK data for each participant and will obtain consensus regarding the safety of continuing the study, the next TPIP dose, and clinical care of the next participant. Expert consultants may be invited to review and interpret participant data. With any safety findings, a decision will be made, based on the review, as to whether enrollment in the study will be allowed to continue. Decisions regarding final database values for PD parameters may be adjudicated by the SRC.

1.2. Schema

1.2.1. Participant Progression Through the Study

The study comprises an outpatient screening period, an inpatient treatment period, and an outpatient follow-up period. Participant progression through the study is shown in Figure 1.

1.2.1.1. Screening Period

The outpatient screening period will last up to 30 days. After participants complete screening and have met the study eligibility criteria, the RHC procedure and inpatient treatment period should be scheduled without delay.

1.2.1.2. Inpatient Treatment Period

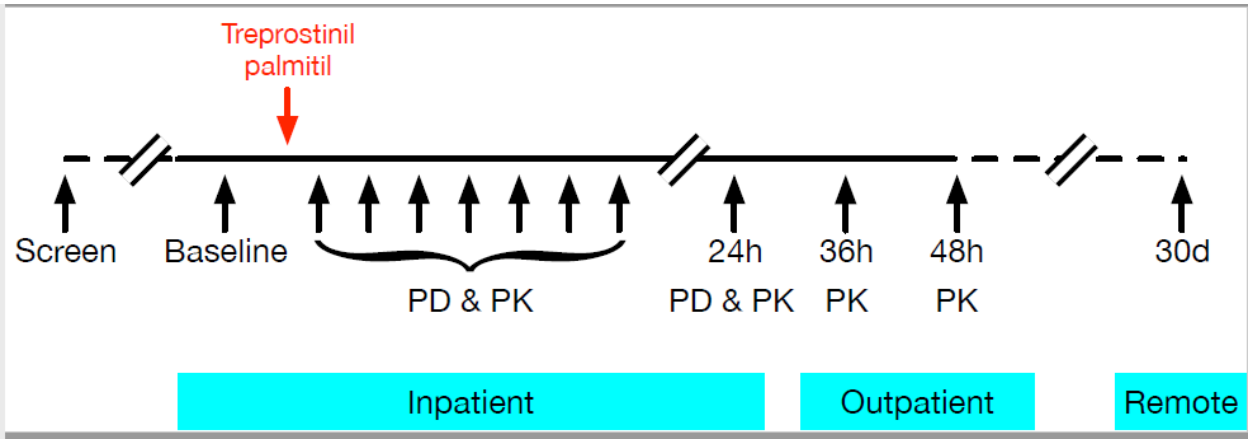
The inpatient treatment period will start on Study Day 1 and extend overnight into Study Day 2. Because the study requires an inpatient treatment period, institutional requirements for elective inpatient admissions, which may vary from site to site, will be followed. The participant may be required to undergo pre-admission assessments required by the institution for elective admission, for example testing for common infectious pathogens. Signature of elective admission documents and other consents may be required by the institution. A right heart catheter (RHC) will be placed. Following completion of Baseline assessments, a single dose of TPIP will be administered via a dry powder inhaler. Safety, PD, and PK assessments will continue at scheduled intervals through 24 hours following TPIP administration. Following the final assessments at 24 hours, the RHC will be removed and the participant will be discharged from the inpatient setting when deemed safe for the participant.

1.2.1.3. Follow-Up Period

PK blood draws for 36 (± 3) hours and 48 (± 4) hours after TPIP dosing will be done on an outpatient basis as arranged by the site. The 48-hour post-TPIP visit will also include safety assessments including physical examination, clinical laboratory evaluations, ECG, AE collection

and vital signs. An additional safety follow-up will be conducted by telephone call or telemedicine on Study Day 30 (± 2 days).

Figure 1: Participant Progression Through INS1009-201 Study



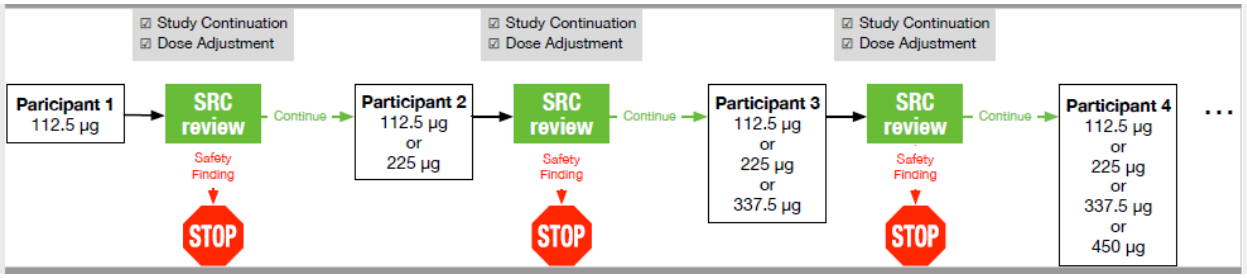
PD-pharmacodynamic assessments; PK=pharmacokinetic assessments; h=hours; d=days

1.2.2. Dose Selection

Each participant will enter the study in a serial fashion, following review of available safety, PK, and PD data from all previous participants by the Safety Review Committee (SRC). Each participant will receive a single-dose administration of TPIP via a dry powder inhaler. TPIP will be administered to only one participant at a time, with full evaluation of all available data prior to dosing the next patient.

The first participant will receive a dose of TPIP containing 112.5 µg of TP. The SRC will then review all available safety, PD, and PK data including data from the first participant and select the TPIP dose and any changes to the assessments for the second participant. Then, following review of all available data including that from the first and second participants, the SRC will select the dose for the third participant. Similarly, all available data from previous studies and participants will be assessed prior to determining the dose for the next participant, until such a time as the SRC believes the study must conclude. Figure 2 describes the planned dose-selection and study continuation process.

Figure 2: Schematic of Study Continuation Planning after Participant 1, INS1009-201



SRC=Safety Review Committee

1.3. Schedule of Activities (SoA)

The SoA is divided into 4 tables:

- Screening and follow-up activities
- Inpatient treatment period
- PK and PD biomarker blood sampling schedule
- Optional procedures and assessments

Table 1: Schedule of Activities for Screening and Follow-up, INS1009-201

Procedure	**Screening**	**Follow-up**	
	Up to 30 Days	**48 h post TPIP dose[a]**	**Study Day 30 (± 2 days)**
Informed Consent	X	--	--
Inclusion/Exclusion Criteria	X	--	--
Demographics and Medical History	X	--	--
Smoking Status	X	--	--
Height, Weight, BMI Calculation	X	--	--
Prior/Concomitant Medications	X	X	X
Serology (HBsAg, HIV antibody, HCV antibody)	X	--	--
Serum Pregnancy Test (WOCBP only)	X	—	—
Urine Pregnancy Test (WOCBP only)	--	—	X
Hematology, Clinical Chemistry (Table 5)	X	X	--
Coagulation Profile (Table 5)	X	--	--
NT-pro-BNP Sample (if needed, Section 5.1)	X	--	--
12-lead ECG	X	X	--
Physical Examination	X	X	--
Vital Signs	X	X	--
6 Minute Walking Distance Test (if needed, Section 5.1)	X	--	--
Pulmonary Function Testing (if needed, (Section 5.1)	X	--	--
Adverse Events[b]	X	X	X

[a] 48 h safety follow-up assessments are to be conducted at the time of the visit for the 48h PK blood draw Table 3)

[b] AE collection is from the time of signing the informed consent through the Day 30 safety follow-up. Events between ICF signing and TPIP dosing that are serious will be recorded as SAE; non-serious events during this period must be recorded as medical history.

Note: Additional safety follow-ups may be conducted at any time per the investigator's discretion to ensure participant safety. The reason for any additional safety follow-up must be reported as an AE

BMI = body mass index; ECG = electrocardiogram WOCBP = woman of childbearing potential;

Table 2: Schedule of Activities for Inpatient Treatment Period, INS1009-201

Treatment Period (StudyDay 1 to Study Day 2)											
	Pre-TPIP Administration	**TPIP Administration**	**Post-TPIP Administration**								
Procedure	Day 1 Baseline	Time 0	30 min	60 min	90 min	2 h	3 h	4 h	8 h	24 h	24 h to discharge
Hematology, clinical chemistry, coagulation profile blood draw[a]	X	--	--	--	--	--	--	--	--	X	--
Urine pregnancy test (WOCBP only)	X	--	--	--	--	--	--	--	--	--	--
12-lead ECG	X	--	--	--	--	--	--	--	--	--	--
Cardiac telemetry per institutional protocol[b]	X	←	—	—	—	—	—	—	—	—	→
Physical Exam	X	--	--	--	--	--	--	--	--	--	X
Vital signs[c]	X		X	X	X	X	X	X	X	X	X
Concomitant medications	X	←	—	—	—	—	—	—	—	—	→
Adverse events collection	X	←	—	—	—	—	—	—	—	—	→
Place right heart catheter	X	--	--	--	--	--	--	--	--	--	--
PD assessments: PVR, MVO_2, Hgb, RVP, PAP CO, PVR, RAP, oxygen consumption, PCWP (Baseline only)[d], heart rate, SpO_2, systemic blood pressure[e]	X	--	X	X	X	X	X	--	X	X	--

Treatment Period (StudyDay 1 to Study Day 2)											
	Pre-TPIP Administration	**TPIP Administration**	**Post-TPIP Administration**								
Procedure	Day 1 Baseline	Time 0	30 min	60 min	90 min	2 h	3 h	4 h	8 h	24 h	24 h to discharge
Administer TPIP	--	X	--	--	--	--	--	--	--	--	--
Remove RHC	--	--	--	--	--	--	--	--	--	--	X
Discharge/Safety Follow-up Instructions	--	--	--	--	--	--	--	--	--	--	X

[a] See Section 10.2 , Table 5 for specific laboratory tests

[b] Routine cardiac telemetry readings will not be collected as study data unless they pertain to a relevant adverse event

[c] Heart rate, systemic blood pressure, and SpO_2 are required PD measurements and will be collected as scheduled. They may be measured with pulse oximetry for heart rate and SpO_2 and an automated inflatable arm cuff for blood pressure. Temperature and respiratory rate may be measured per institutional inpatient protocol. Respiratory rate will be measured as part of pulmonary gas exchange testing, if performed (Table 4)

[d] PCWP is measured at Baseline only to ensure study eligibility (Section 5.1).

[e] Systemic blood pressure must include 3 values: systolic, diastolic, and mean arterial pressure.

CO = cardiac output; Hgb = hemoglobin; MVO_2 = mixed venous oxygen saturation; PAP = pulmonary arterial pressure; PVR=pulmonary vascular resistance; RAP = right atrial pressure; RVP = right ventricular pressure;SpO_2 = arterial blood oxygen saturation; WOCBP = woman of childbearing potential

Table 3: PK and PD Biomarker Sampling Schedule, INS1009-201

--	**Baseline Pre-TPIP Administration**	**TPIP administration**	**Post-TPIP Administration**							
Time	--	0	30 (± 10) mins	60 (± 10) mins	2 h (± 20 mins)	4 (± 1) h	8 (± 2) h	24 (± 2) h	36 (± 3) h	48 (± 4) h
PK sampling[a] [b]	X	--	X	X	X	X	X	X	X	X
Sample to be frozen for biomarker analysis[c]	X	--	--	--	--	X	X	--	--	--

[a] PK sampling for treprostinil palmitil and treprostinil

[b] Each PK sample will be approximately 10 mL

[c] Each biomarker sample will be approximately 5 to 7 mL

Table 4: Schedule for Echocardiogram, Pulmonary CT Scan, and Resting Respiratory Gas Exchange Assessments, Inpatient Treatment Period, INS1009-201

Inpatient Treatment Period (Study Day 1 to Study Day 2)										
	Pre-TPIP Administration	**TPIP Administration**	**Post-TPIP Administration**							
Procedure	StudyDay 1 Baseline	Time 0	2-8 hr	4-8 hr						
Transthoracic echocardiogram (LVEF,TVR maximum velocity, TAPSE, end diastolic right ventricular volume)	X	--	X	--						
Pulmonary CT scan (total blood volume, blood volume in vessels < 5 mm^2)	X	--	--	X						
--	**Pre-TPIP Administration**	**TPIP Administration**	--							
--	Study Day 1 Baseline	Time 0	30 mins	60 mins	90 mins	2 h	3 h	4 h	8 h	24 h
Resting respiratory gas exchange assessment[a] (respiratory rate, minute ventilation, VCO_2, ETO_2, $ETCO_2$, SpO_2	X	--	X	X	X	X	X	--	X	X

[a] Resting respiratory gas assessment parameters are collected at the same time points as RHC parameters

NOTE: Parameters to be measured for each procedure are in parentheses

CT=computerized tomography; $ETCO_2$ =end tidal carbon dioxide concentration; ETO_2,=end tidal oxygen concentration; LVEF=left ventricular ejection fraction; SpO_2=arterial blood oxygen saturation; TAPSE=tricuspid annular plane systolic excursion; TVR=tricuspid valve regurgitation; VCO_2,=carbon dioxide production

2. INTRODUCTION

Pulmonary hypertension (PH), a hemodynamic state characterized by resting mean PAP ≥ 25 mmHg, is generally classified into 5 groups based on the underlying pathology: Group 1 is PH due to pulmonary vascular disease, also known as PAH; Group 2 is PH due to left heart disease; Group 3 is PH due to lung disease or hypoxia; Group 4 is PH due to chronic thromboembolic disease or other pulmonary vasculature obstruction; Group 5 is miscellaneous PH syndromes caused by a variety of disorders such as hemolytic anemias and sarcoidosis (Thenappan et al., 2018).

In Group 1 PH (PAH), the resting mean PAP ≥ 25 mmHg occurs in the setting of normal pulmonary arterial wedge pressure of ≤15 mm Hg with PVR of ≥3 Wood Units (WU) (McLaughlin et al., 2009). In PAH the pulmonary vasculature is affected by vasoconstriction, vascular remodeling, increased rigidity of vessel walls and vascular fibrosis. These vascular anomalies increase PVR, which leads to increases in right ventricular afterload, and a cascade of maladaptive changes to the heart including right ventricular hypertrophy, ischemia and fibrosis, reducing right ventricular function and eventually leading to right ventricular failure and death (Thenappan et al., 2018). The pulmonary vascular lesions of PAH may be idiopathic, hereditary, or occur as a complication of drug use (eg, anorexigens), connective tissue disease, portal hypertension, congenital cardiac malformations or HIV infection (Hoeper et al., 2017).

Data from PAH registries around the world (Thenappan et al., 2018) estimate a global incidence ranging from 2.0 to 7.6 cases per million adults per year, with a prevalence of 11 to 26 cases per million adults; the incidence in females is approximately 4 times that in males. Most registries report a mean age of onset ranging from approximately 36 to 53 years. While overall median survival has improved from 2.8 years in the 1980's to 6 years currently, mortality is high, with 1 year survival ranging from 68% to 93% and 5 year survival ranging from 21% to 65%. Nearly half of the patients in these registries have PAH of idiopathic, heritable or anorexigen-induced origin.

PAH is a debilitating progressive disease that causes a wide range of non-specific symptoms including, dyspnea, shortness of breath, chest pain, fatigue, generalized weakness and exertional syncope (Delcroix and Howard, 2015), severely affecting the patient's physical mobility, emotional and social well-being, ability to perform activities of daily living and overall quality of life. Pharmacological treatments are available to mitigate disease symptoms and slow disease progression, but treatment-related AEs, inconvenience and side effects can be treatment-limiting and negatively influence the patient's daily life (Delcroix and Howard, 2015).

The currently available pharmacologic treatments for PAH include calcium channel blockers, guanylate cyclase stimulators, endothelin receptor antagonists, phosphoesterase type 5 inhibitors, and prostanoids and prostacyclin agonists. Prostanoids, such as TRE, are among the most effective medications for the treatment of PAH. However, they are limited by the need for inconvenient and frequent drug administration and dose-limiting side effects (Thenappan et al., 2018)

2.1. Study Rationale

Treprostinil palmitil (TP) is an inactive prodrug of TRE. TPIP is a dry powder for inhalation formulation of TP. TPIP is being developed for the treatment of PAH. TPIP is expected to provide extended release of TRE in the lung with the goals of less frequent and more convenient and consistent dosing while reducing the frequency and severity of dose-limiting side effects associated with the currently approved forms of TRE. TP has been previously studied in healthy volunteers as an inhalation suspension (treprostinil palmitil inhalation suspension, TPIS), in single doses up to 340 µg (Study INS1009-101). TPIP is being studied in a SAD/MAD study in healthy volunteers (Study INS1009-102).

No studies of TP or TPIP have been conducted in patients with PAH. Study INS1009-201 is an open label, non-randomized, single- dose study designed to evaluate the safety, pharmacokinetics (PK), and pharmacodynamic (PD) effects of a single dose of TPIP in patients with PAH.

2.2. Background

Treprostinil is a tricyclic benzidene analogue of prostacyclin. As such, TRE has vasodilatory and anti-platelet activity within the pulmonary vascular system, thereby reducing blood flow resistance and improving the clinical state, functional class, exercise capacity, and quality of life of patients with PAH (Vachiery and Naeije, 2004).

Treprostinil has a high potency but is short-lived in the body and must be administered by continuous IV or SC infusion, or given multiple times per day by inhaled or oral routes. At present, TRE is available in the United States in formulations of IV or SC infusion (Remodulin Package Insert, 2018), oral extended-release tablets (Orenitram Package Insert, 2019), and inhalation solution (Tyvaso Package Insert, 2017) to treat PAH. The clinical experience with TRE suggests that most of the AEs experienced are related to its effects on prostanoid metabolism (eg, headache, nausea, diarrhea, flushing, and hypotension). Dose-limiting side effects correlate to systemic plasma concentrations of TRE.

Treprostinil palmitil is a hexadecyl ester prodrug of TRE. In the lung, TP is hydrolyzed by esterase to TRE and hexadecanol. TPIP is a dry powder formulation of TP designed to provide sustained release of TRE in the lung over a prolonged period, thus providing prolonged vasodilation in the lung vasculature. This effect was demonstrated in a rat acute hypoxia model that showed a maximal reduction in PAP through the 3-hour monitoring limit with TP, while the effect of inhaled TRE started to diminish by 1 hour and was completely gone after approximately 2.5 hours. The prolonged lung exposure and pharmacological action of TRE achieved with sustained release from the prodrug TP aims to reduce both dosing frequency and side effects driven by fluctuations of plasma levels of TRE.

Treprostinil palmitil was well tolerated in rats and dogs following 16-week once-daily inhalation. At NOAEL doses, the plasma C_{max} and AUC of TRE at steady state in rats (2000 µg/kg/day) were 11 ng/mL and 73 ng*h/mL, respectively, and in dogs (250 µg/kg/day) were 1.2 ng/mL and 13 ng*h/mL, respectively.

Treprostinil palmitil has been administered to adult healthy volunteers as a nebulized inhalation suspension (TPIS) in a SAD clinical study (Study INS1009-101) that compared TP inhalation at ascending doses (85 to 340 µg) with a Tyvaso® inhalation dose of 54 µg. PK data from this study

demonstrated that TPIS provided a longer duration of TRE exposure than Tyvaso inhalation. With TP inhalation, TRE exposures increased approximately dose proportionally with increasing dose. The mean (%CV) of plasma C_{max} for TRE ranged from 89 to 318 pg/mL (24.9% to 49.2%) across doses and the TRE AUC ranged from 674 to 2490 pg*h/mL (7.8% to 24.3%) across doses. The t_{max} was 0.8 to 2 hours and the $t_{1/2}$ was approximately 7 hours. The TP plasma concentrations were low with AUC approximately 7-fold lower than that for TRE. Following Tyvaso inhalation at 54 µg, TRE C_{max} was 958 pg/mL (26.5%), AUC_{0-24} was 872 pg*h/mL and $t_{1/2}$ was 0.485 hour.

Additional information regarding the results of non-clinical and clinical studies of TP are provided in the Investigators' Brochure.

2.3. Benefit/Risk Assessment

Detailed information about the known and expected benefits and risks and reasonably expected TEAEs for TPIP from clinical and non-clinical studies may be found in the Investigator's Brochure.

2.3.1. Risk Assessment

There is no TPIP experience in patients with PAH, however, the active component, TRE, like other prostanoids and their agonists, has a well-characterized safety profile. This will help enable participants to be adequately monitored during the study.

The Insmed has conducted a SAD study of TPIS in healthy volunteer participants, with safety and tolerability findings similar to those of other prostanoids (Study INS1009-101). In this study, 32 TEAEs were reported for 11 of 18 participant who received TPIS. No fatal TEAEs were reported and no TEAEs led to the withdrawal of participants. One participant who received a single dose of TPIS containing 340 µg of TP experienced several interrelated AEs that culminated in 2 TEAEs of severe and life-threatening intensity. The Investigator believed a severe TEAE of micturition syncope was precipitated by a TEAE of chest pain, which was assessed as probably related to the study IMP and increased vagal tone during micturition. Follow-up evaluation by an external cardiologist reveled that the participant had Tachy-Brady syndrome. An SAE of cardiac pause/nodal arrhythmia was reported for this participant and assessed as probably related to TPIS. Beyond this event, 7 TEAEs were assessed as being of moderate intensity and 23 TEAEs to be of mild intensity.

The most frequently reported TEAEs among participants receiving TPIS were cough (5 events for 5 participants), dyspnea (4 events for 4 participants) and throat irritation (4 events for 4 participants. Other TEAEs reported for more than 1 participant receiving TPIS included nausea (3 events for 3 participants) and headache (2 events for 2 participants).

There was a dose-related trend in the incidence of TEAE reporting with increasing dose levels of TPIS: 5 TEAEs were reported for 2 participants after receiving a single TPIS dose containing 85 µg of TP, 7 TEAEs were reported for 4 participants after receiving a single TPIS dose containing 170 µg of TP, and 20 TEAEs were reported for 5 participants after receiving a single TPIS dose containing 340 µg of TP.

Available safety, PK, and PD data from a recently conducted SAD/MAD study of TPIP in healthy volunteer participants (INS1009-102) will inform the TPIP dosing and management of

participant safety for this study. In Study INS1009-102 TPIP single doses of 112.5, 225, 450, and 675 µg are being evaluated. Data were still blinded at the time of protocol finalization.

No serious adverse reactions are considered expected for TPIP. Please refer to the Reference Safety Information in Section 6.1 of the Investigator's Brochure.

Risks inherent in study procedures and in the inpatient treatment period will be managed per Investigator and institutional processes. It is possible that the RHC-dependent Baseline parameters may indicate that the participant does not meet study inclusion criteria, may meet exclusion criteria, or is otherwise not suitable for study participation; in this case the Investigator may end the RHC procedure and not administer TPIP.

In general, an RHC is left in place for 30 to 60 minutes to take necessary measurements. This study requires the RHC to be in place for approximately 24 hours. Excess risks with prolonged placement of the RHC may include but not be limited to dislodging of the RHC, infection, bleeding, and participant discomfort.

2.3.2. Benefit Assessment

Participants in this study are not expected to receive any clinical benefit.

2.3.3. Overall Benefit: Risk Conclusion

Although participants are not expected to benefit individually from this study, risks to their well-being will be carefully monitored and managed throughout their participation. The Insmed considers the risks to be appropriate to the value of the knowledge gained in this study about the characteristics of this promising therapy. The well-characterized safety profile of TRE and the inpatient treatment and observation period will enable participants to be adequately monitored during the study. Most TEAEs observed with exposure to this drug are events known to be associated with prostanoids and their agonists. Study inclusion and exclusion criteria will help to ensure that only appropriate participants are enrolled. Risks involved with study procedures and settings will be managed by the relevant Investigator and institutional processes.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	**Primary**
• To evaluate the safety and tolerability of single doses of TPIP in participants with PAH	• Frequency of TEAEs
Secondary	**Secondary**
• To evaluate the effects of single doses of TPIP on PVR in participants with PAH over the first 24 hours following administration	• Change from Baseline in PVR at 8 and 24 hours after TPIP administration
• To evaluate the PK of TRE in participants with PAH	• C_{max}, t_{max}, $AUC_{t1–t2}$, $AUC_{0–\infty}$, $t_{1/2}$ of TRE in plasma
Exploratory	**Exploratory**
• To evaluate the PD effects of single doses of TPIP in participants with PAH over 24 hours following administration	• Change from Baseline in PVR, PAP, RVP, RAP, CO, oxygen consumption, MVO_2, SpO_2, heart rate, systemic blood pressure, hemoglobin, at selected timepoints after TPIP administration
• To evaluate the effect of single doses of TPIP on selected biomarkers in participants with PAH over 24 hours following administration	• Change from Baseline in selected biomarker concentrations at selected time points after TPIP administration
• To evaluate changes in clinical laboratory parameters in participants with PAH after TPIP administration	• Clinically relevant change from Baseline in hematology, coagulation and clinical chemistry parameters (Section 10.2, Table 5)
• To evaluate the PK of TP in participants with PAH • To evaluate the PK of TRE in participants with PAH	• Plasma PK parameters of TP, such as C_{max}, t_{max}, $AUC_{t1–t2}$, $AUC_{0–\infty}$, $t_{1/2}$, CL/F and Vd/F • Plasma PK parameters of TRE, such as C_{max}, t_{max}, $AUC_{t1–t2}$, $AUC_{0–\infty}$, $t_{1/2}$, CL/F and Vd/F

• To evaluate the effects of TPIP on resting respiratory gas exchange in participants with PAH[a]	• Change from Baseline in respiratory rate, minute ventilation, VCO_2, ETO_2, $ETCO_2$, SpO_2 over 24 hours after TPIP administration
• To evaluate the effects of TPIP on parameters of right ventricular function in participants with PAH as measured by transthoracic echocardiogram[b]	• Change from Baseline in LVEF, TVR maximum velocity, TAPSE, and end diastolic right ventricular volume at 2 to 8 hours after TPIP administration
• To evaluate the effects of TPIP on pulmonary vasculature and blood flow parameters in participants with PAH as measured by pulmonary CT scan[c]	• Change from Baseline in total blood volume, blood volume in vessels < $5mm^2$ at 4 to 8 hours after TPIP administration

[a] Respiratory gas exchange testing optional at investigator discretion

[b] Echocardiogram optional at investigator discretion

[c] Pulmonary CT scan optional at investigator discretion

$AUC_{0-\infty}$ = area under the concentration time curve from time zero to infinity; AUC_{t1-t2} = area under the concentration time curve from time zero to last sampling timepoint with measurable concentration; C_{max} = maximum observed concentration after drug administration; CL/F = apparent total clearance; CO = cardiac output; CT = computerized tomography; $ETCO_2$ = end tidal carbon dioxide concentration; ETO_2 = end tidal oxygen concentration; LVEF = left ventricular ejection fraction; MVO_2 = mixed venous oxygen saturation; PAH = pulmonary arterial hypertension; PAP = pulmonary arterial pressure; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PVR = pulmonary vascular resistance; SpO_2 = arterial blood oxygen saturation; TAPSE = tricuspid annular plane systolic excursion; TEAE = treatment emergent adverse event; TP = treprostinil palmitil; TPIP = treprostinil palmitil inhalation powder; TRE = treprostinil; TVR = tricuspid valve regurgitation; t_{max} = time of maximum observed concentration following drug administration; $t_{1/2}$ = elimination half-life; Vd/F = apparent volume of distribution at terminal phase; VCO_2 = carbon dioxide production

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2a, open label, non-randomized single-dose study to assess the safety, tolerability, PD effects and PK of TPIP administered to participants with WHO Group 1 PH (PAH). This is the first patient study of TPIP. Each participant will receive a single dose of TPIP. The first participant will receive a dose containing 112.5 µg of TP. The TP dose level for each subsequent participant will be determined following review and adjudication of all available safety, PK, and PD data from the previous participant(s)by the SRC (Section 10.1.7).

This is a "proof of mechanism" study designed to investigate the following:

1. The safety and tolerability of TPIP in participants with PAH,
2. The relationship between the PK and PD effects of TPIP in participants with PAH, and
3. The duration of the PD effects of a single dose of TPIP in participants with PAH.

The cardiopulmonary and overall functional status of patients with PAH can be labile and medical instability can develop quickly. The study is designed to provide maximal safety and minimal risk to participants. As such, there considerable flexibility built into the protocol to allow Investigator discretion with the frequency, timing, and/or conduct of PD and PK assessments to ensure participant safety. Because the study requires an overnight inpatient treatment period, Institutional requirements for elective inpatient admissions, which may vary from site to site, will be followed.

For individual participants, the study will consist of an outpatient screening period lasting up to 30 days. The inpatient treatment period will start on Study Day 1 and is expected to last overnight into Study Day 2. Outpatient PK sampling and safety follow-up at 36 (± 3) and 48 (± 4) hours post TPIP dose will extend into Study Day 3. A remote safety follow-up visit is scheduled for Study Day 30 (± 2 days).The 48 hour PK visit will also include safety assessments including ECG, clinical laboratory evaluations, vital signs, physical examination, and AE collection (Table 1). The safety follow-up period will conclude with a remote (telephone or telemedicine) visit on Study Day 30 (± 2 days). Including the Screening, Treatment, and Follow-Up Periods, the study participation period is expected to be 62 days or less. Any study-related safety issues that extend past Study Day 30 will continue to be followed until they resolve.

4.1.1. Screening Period

The screening period will be up to 30 days. Required Screening assessments are shown in Table 1. Participants who fail one or more screening assessments may be re-screened once at the Investigator's discretion in order to meet study entry criteria. See Section 5.4 for additional information regarding participants who fail screening and/or are re-screened.

4.1.2. Inpatient Treatment Period

4.1.2.1. Baseline Procedures and Assessments

The inpatient treatment period will be on Study Days 1 and 2. The participant may be required to undergo pre-admission assessments required by the Institution for elective admission, for example testing for common infectious pathogens. Signature of Institutional elective admission documents and consents to procedures may be required. Data from required institutional assessments and consents will not be routinely collected as part of study data unless they pertain to a relevant AE or study endpoint.

Participants will be admitted to an inpatient care setting such as an ICU, cardiac catheterization laboratory or other similar setting. They will have Baseline laboratory and safety assessments as shown in Table 2. A RHC will be placed for Baseline assessment of cardiopulmonary hemodynamics prior to TPIP administration and intermittent assessments of cardiopulmonary hemodynamics for 24 hours following TPIP administration. Institutional procedures and protocols for placement, care, monitoring, and removal of the RHC will be carried out but will not be collected as study data unless relevant.

Some procedures and assessments for exploratory endpoints may not be offered at all sites. Participants will be asked to give informed consent only to those procedures that are being conducted by their Investigator at their site. These procedures include the following:

- Transthoracic echocardiogram at Baseline and during a 2 to 8 hour window after TPIP administration (Table 4).
- Pulmonary CT scan at Baseline and during a 4 to 8 hour window after TPIP administration (Table 4).
- Resting respiratory gas exchange assessment at Baseline and intermittently after TPIP administration for up to 24 hours (Table 4). Resting respiratory gas exchange assessments will be standardized, with all participating investigators using similar equipment and procedures.

For example, an Investigator who is doing only RHC and resting respiratory gas exchange assessments for this study will obtain informed consent for those procedures only and will not offer or ask the participant for informed consent for transthoracic echocardiogram or pulmonary CT scan as part of this study.

Following completion of all Baseline assessments, including Baseline blood draws for PK and PD biomarkers (Table 3), the prescribed single dose of TPIP will be administered (Table 2).

4.1.2.2. Post-TPIP Administration

Following TPIP administration, participants will have intermittent safety, clinical laboratory, PK, and PD assessments, as specified in the SoA (Table 2 Table 3 Table 4). The study is designed to allow maximum flexibility for interventions and assessments at the discretion of the Investigator and institutional policies and procedures to ensure participant safety. At any time, the investigator has the option to discontinue assessments for participant safety or tolerability reasons. Additional laboratory and/or hemodynamic assessments may be performed as deemed necessary for participant safety. Following completion of scheduled events, the investigator has

the option of continued laboratory and/or hemodynamic monitoring as deemed appropriate for participant safety.

If, in the interest of participant safety, the Investigator omits scheduled assessments/procedures or performs additional assessments/procedures, the reason for doing so must be reported on the CRF as an AE in order to avoid a protocol violation.

Following completion of protocol-required assessments and removal of the RHC, the participant will be discharged from the inpatient setting when deemed safe by the Investigator. Investigator and institutional usual care protocols for patient discharge and follow-up for an RHC procedure will apply.

4.1.2.3. Post-discharge Outpatient Visits for PK Sampling and Safety Follow-up

The participant will be required to return as an outpatient for the 36 (± 3) and 48 (± 4) hour post TPIP administration PK samples. Additional safety assessments such as ECG, physical examination, vital signs, AE collection, and clinical laboratory evaluations will be completed at the 48 hour visit. Female participants who are WOCBP will be given a self-administered pregnancy test kit with instructions to self-administer the test and report the results on the day of the Study Day 30 safety follow-up visit (Section 4.1.3).

4.1.3. Safety Follow-up

A remote (telephone call or telemedicine) safety follow-up visit is scheduled for Study Day 30, at which time participants who are WOCBP will also be asked to report the results of the self-administered pregnancy test they were given at the 48 hour post-TPIP follow-up visit (Section 4.1.2.3, Table 1).

4.2. Scientific Rationale for Study Design

The study is designed to understand the safety and acute PK and PD effects of TPIP in participants with PAH, the intended patient population. Intensive monitoring via RHC in an appropriate inpatient setting is essential to understand how TPIP affects cardiopulmonary hemodynamics and to elucidate relationships between dose, PK, and PD effects. Some assessments and study activities for exploratory endpoints are considered optional depending on Investigator preference and/or based on study site capabilities and procedures (Table 4).

4.3. Justification for Dose

Treprostinil palmitil has been previously studied in healthy volunteer participants as a liquid suspension for inhalation (TPIS) and has now been formulated as a dry powder for oral inhalation (TPIP). Data from pre-clinical pharmacology and safety studies supported the initiation of human studies with TPIS. Preclinical studies in rats and dogs showed that the plasma kinetics of TRE and TP after dosing with TPIP are similar to those of TPIS. For further information on the non-clinical pharmacology and safety studies of TPIS and TPIP, please refer to the Investigator's Brochure.

The selection of TP dose levels for this study was primarily based on the safety and tolerability of TPIS in healthy participants following single dose inhalation at 85 to 340 µg (Study INS1009 101).The starting dose of 85 µg TP administered as TPIS in Study INS1009-101 was

selected as molar equivalent to the single dose of TRE in Tyvaso. Based on the formula used to predict the human equivalent dose from animal dose and animal weight (US Food and Drug Administration, 2005), this dose is 4-fold lower than the calculated maximum safe starting dose of 324 µg and 3-fold lower than the calculated human lung-equivalent dose of 255 µg. A safety factor of less than 10 was considered appropriate in selection of this dose as TRE is a member of a well-characterized class of compounds (prostanoids) and has been previously studied in 4 different formulations (inhaled, SC, IV, and oral) (Remodulin Package Insert, 2018), oral extended-release tablets (Orenitram Package Insert, 2019), and inhalation solution (Tyvaso Package Insert, 2017).

The current study utilizes the clinical experience of TPIS from Study INS1009-101 in healthy volunteer participants and the ongoing INS1009-102 SAD/MAD study of TPIP in healthy volunteer participants. In Study INS1009-101, doses of TPIS were administered in multiples of 85 µg TP to include 170 µg (2 × 85 µg) and 340 µg (4 × 85 µg) of TP. The systemic exposure for TRE at 340 µg TP was low (AUC < 2.5 ng*h/mL) with an elimination $t_{1/2}$ of approximately 7 hours. In the first SAD portion of INS1009-102 (SAD1) 18 participants were randomized to 1 of 3 TP dose levels of TPIP: 112.5 µg, 225 µg, or 450 µg of TP (6 participants at each dose). Preliminary concentration data for this cohort, when normalized by dose, appear to be similar to those from Study INS1009-101, suggesting a similar bioavailability in humans between TPIP and TPIS. The safety and PK results of single doses of the 3 dose levels of TPIP in the 18 healthy participants will inform dosing in the current study.

Administration of TPIP will be via inhalational dry powder packaged in single actuation capsules. Each capsule contains 7.5 mg of dry powder, containing 112.5 µg of the TP prodrug, the molar equivalent of 71 µg of TRE. It is expected that about 85 µg of TP (54 µg of TRE equivalent) will be emitted from the dry powder inhalation device. This is comparable to a single administration of Tyvaso for patients with PAH with the target dose being 54 µg QID. Single doses of up to 90 µg of Tyvaso have been administered in clinical studies of healthy volunteer participants (Tyvaso Package Insert, 2017).

Each participant will receive a single dose administration of TPIP. A TPIP dose containing 112.5 µg of TP will be given to the first participant in Study INS1009-201. All available data (PD, PK, safety) from the first participant will be assessed and evaluated by the SRC, as well as available data from the ongoing INS1009-102 study. Following this evaluation, the SRC will determine if it is safe to continue the study, the TPIP dose level and any changes to safety PD and PK assessments for the second participant (Figure 2). This process will be repeated using the total accrued data of all completed participants prior to determining the TPIP dose for each subsequent participant. There will be no simultaneous dosing of participants; each participant will be treated as an individual case for evaluation. The TP dose level for each subsequent participant may be increased, held stable or lowered, depending on the accumulating data from previous participants. TPIP doses containing < 112.5 µg TP will not be used. TPIP dosing may be stopped at any dose level as determined by the SRC.

4.4. Study Completion

A participant will be considered to have completed the study if he/she has completed all phases of the study including the Study Day 30 safety follow-up (the last scheduled procedure shown in Table 1).

The study will be considered completed on the date of the last safety follow-up of the last participant in the study.

5. STUDY POPULATION

The study is expected to recruit approximately 6 to 10 participants at up to 4 centers with appropriate inpatient facilities in the United States. Eligible participants must have clinically stable disease of mild to moderate severity, with good to moderate functional status. Participants may not be taking more than 2 medications from the following classes:

- Endothelin receptor antagonists (eg ambrisentan, bosentan, macitentan),
- Phosphodiesterase type 5 inhibitors (eg sildenafil, tadalafil)
- Guanylate cyclase stimulator (eg riociguat)

It is expected that the site will recruit appropriate potential participants according to the criteria in Section 5.1 and Section 5.2. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

The study inclusion and exclusion criteria include thresholds of selected RHC and ECG parameters that must be met at Baseline or the participant will not be considered eligible for the study. In this case, the participant is to be reported as a Screen Failure (Section 5.4).

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if they meet all of the following criteria:

Age:
1. Participant must be ≥ 18 years of age at the time of signing the informed consent.
Type of Participant and Disease Characteristics
2. Participants must have a diagnosis of WHO Group 1 PH (PAH) with the following characteristics (Galie et al., 2016): a. Etiology of idiopathic, heritable, drug/toxin-induced or connective tissue disease (CTD)-related PAH; b. Right heart catheterization within the last 3 years with the following hemodynamic findings: - Mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg at rest, - Pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg, and - Pulmonary vascular resistance (PVR) of ≥ 3 Wood Units (WU) 3. PAH diagnosis for at least 1 year and less than 10 years 4. New York Heart Association (NYHA)/WHO Functional capacity Class II-III 5. No change in pulmonary hypertension medications (eg, ambrisentan, bosentan, macitentan, sildenafil, tadalafil, riociguat) or dosage for at least 90 days prior to Screening. 6. No change in diuretic use or dosage for at least 30 days prior to Screening

7. Documented predicted percent forced vital capacity (FVC) > 70% within 1 year of Screening. If not available, pulmonary function testing will be performed at Screening (Table 1)
8. At least 2 of the following European Respiratory Society/European Society for Cardiology (ERS/ESC) low risk criteria:
    a. NT-pro-BNP concentration < 300 ng/L within 6 months of Baseline (if not available will be obtained at Screening, Table 1)
    b. Historical documentation of 6- minute walk distance (6MWD) > 440 meters within 6 months prior to Baseline. If not available will obtain 6MWD test at Screening (Table 1)
    c. Right atrial pressure (RAP) < 8 mmHg within 1 year prior to Baseline
    d. Cardiac Index (CI) ≥ 2.5 L/min*m^2or mixed venous oxygen saturation (MVO_2) > 65% within 1 year prior to Baseline
9. Right heart catheterization at Baseline with the following hemodynamic findings:
10. Mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg at rest,
11. - Pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg, and
12. - Pulmonary vascular resistance (PVR) of ≥ 3 Wood Units (WU)

Weight

13. Body mass index (BMI) within the range 19.0 - 32.0 kg/m^2 (inclusive).

Sex and Contraceptive/Barrier Requirements

14. Male participants: Male participants and their female partners of childbearing potential must agree to use highly effective contraception from Study Day 1 to at least 90 days after dosing.
15. Female participants: Women of child-bearing potential (WOCPB, defined as premenopausal, not surgically sterile for at least 3 months prior to Screening) must use a highly effective contraception method and agree to be tested for pregnancy from at Screening, Baseline, and 30 days after dosing.

See Section 10.4 for contraceptive guidance.

Informed Consent

16. Capable of giving signed informed consent as described in Section 10.1.5 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if they meet any of the following criteria:

Medical Conditions

1. Any PH other than idiopathic, hereditary, drug/toxin-induced, or connective tissue disease (CTD) associated PAH (eg, congenital heart disease-associated PAH, portal hypertension-associated PAH, PH belonging to Groups 2 through 5)
2. Allergy, or documented hypersensitivity or contraindication, to the ingredients of treprostinil palmitil inhalation powder (TPIP) or treprostinil (TRE).
3. Previous intolerance to prostacyclin analogs or receptor agonists (eg, selexipag) per investigator discretion
4. History of anaphylaxis or previously documented hypersensitivity reaction to any drug per Investigator discretion
5. QTcF interval > 480 ms on resting ECG at Baseline
6. History of heart disease including left ventricular ejection fraction (LVEF) ≤ 40% or clinically significant valvular, constrictive, or atherosclerotic heart disease (myocardial infarction, etc)
7. Abnormal renal function (estimated glomerular filtration rate < 30 mL/min/1.73m^2) at Screening.
8. Active liver disease or hepatic dysfunction manifested as:
    a. Elevated liver function test results (ALT or AST > 2 × ULN) at Screening
    b. Bilirubin > 1.5 × ULN (isolated bilirubin > 1.5 × ULN; ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%) at Screening.
    c. Known hepatic or biliary abnormalities, not including Gilbert's syndrome or asymptomatic gallstones at Screening.
9. History of HIV infection/positive HIV serology test result at Screening.
10. History of active/chronic Hepatitis B or C/ positive hepatitis B or C serology test result at Screening
11. History of abnormal bleeding or bruising.
12. Known or suspected immunodeficiency disorder, including history of invasive opportunistic infections (eg, tuberculosis, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis) despite infection resolution, or otherwise recurrent infections of abnormal frequency, or prolonged infections suggesting an immune-compromised status, as judged by the investigator.
13. Active and current symptomatic infection by SARS CoV 2. Additional COVID 19 restrictions per institutional guidelines (See also Section 10.1.3.1.3)
14. Patients with current or recent (past 4 weeks) lower respiratory tract infection (may be re-screened at appropriate time (Section 5.4)

15. History of malignancy in the past 5 years, with exception of completely treated in situ carcinoma of the cervix and completely treated non-metastatic squamous or basal cell carcinoma of the skin.
Concomitant Therapy
16. Patients receiving triple combination therapy for PAH consisting of endothelin receptor agonists, phosphoesterase type 5 inhibitors, and guanylate cyclase stimulators (riociguat). 17. Patients receiving prostanoids/prostacyclin agonists 18. Other prior/concomitant therapies are allowed/disallowed at the Investigator's discretion
Prior/Concurrent Clinical Study Experience
19. Have participated in any other interventional clinical studies within 30 days of Baseline
Diagnostic assessments
20. Any clinically significant abnormal laboratory, value, test result, or physical examination finding at Screening; diseases or diagnoses/disorders that, in the opinion of the Investigator, may put the participant or others at risk by participating in the study, interfere with the participant's treatment and assessment, or influence the results of the study; or have compliance issues with the study.
Other Exclusions 21. Current or history of substance and/or alcohol abuse per Investigator assessment 22. Current user of cigarettes or e-cigarettes **23.** Pregnant or breastfeeding.

5.3. Lifestyle Considerations

No lifestyle restrictions are required.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study because they did not meet all inclusion criteria or meet one or more exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once at the Investigator's discretion. If a participant can be rescreened, the PI is to

consult with the Medical Monitor to determine whether some or all of the Screening assessments must be repeated. Rescreened participants will sign a new ICF and will be assigned a new participant number.

5.5. Criteria for Temporarily Delaying Inpatient Treatment Period

Following successful screening and meeting of study eligibility criteria, the inpatient treatment period and RHC procedure must be scheduled without delay.

The scheduled treatment period may be temporarily delayed no longer than 28 days by the Investigator in consultation with the Medical Monitor for valid reasons. Examples of valid reasons for delaying the treatment period may include such things as a life event for the participant (eg death in the family), local public health emergency (eg, COVID 19 outbreak), site facility issues (eg, catheterization lab or ICU bed availability), or pending TPIP dosing directives from the SRC.

A temporary delay in the scheduled inpatient treatment period for a valid reason may result in previously met Inclusion Criteria that rely on a time window to be not met (eg, 6MWD falls outside the 6 months prior to Baseline window). This is not considered to be a Screen Failure. In this case, the Investigator should consult with the Medical Monitor to identify which Screening tests need to be conducted or repeated to ensure that the participant meets study inclusion criteria and can safely participate in the study.

Deterioration of the participant's medical condition is not a valid reason to delay start of the inpatient treatment period. In some cases delaying the inpatient treatment period may cause the participant to meet one or more exclusion criteria (eg, participant develops a lower respiratory infection). In this case the participant should be considered a Screen Failure and Section 5.4 applies.

6. STUDY IMP AND CONCOMITANT THERAPY

Study IMP is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study IMP Administered

A single dose of TPIP is the only study IMP. Each TPIP capsule contains 7.5 mg of dry powder, containing 112.5 µg of the TP prodrug. A dose may consist of a single capsule or of multiple capsules administered in succession.

Name of Treatment	Dose	Supplied Formulation	Route and Frequency of Administration
Treprostinil palmitil inhalation powder (TPIP)	One or more single actuation capsules	Single actuation capsules containing 112.5 µg TP per 7.5 mg powder	Single dose after Baseline assessments

6.1.1. Medical Devices

In the planned clinical study, the TPIP will be administered by oral inhalation using a Plastiape capsule-based Dry Powder Inhaler (RS 01 Mod 7). A Type III Drug Master File is filed at the US FDA and the RS01 inhaler is classified as a Class I medical device. The Instructions for Use of the device document is provided separately as an Appendix to the Pharmacy Manual.

All device deficiencies (including malfunction, use error, and inadequate labeling) shall be documented and reported by the investigator throughout the clinical investigation (Section 8.3.8) and appropriately managed by Insmed.

6.2. Preparation/Handling/Storage/Accountability

Insmed Incorporated will provide the investigator and clinical unit with adequate quantities of TPIP capsules. TPIP-filled HPMC capsules will be delivered in HDPE bottles overwrapped with an aluminum pouch, containing a sachet of desiccant to prevent moisture ingress. The powder will be administered by oral inhalation using a Plastiape capsule-based Dry Powder Inhaler (Section 6.1.1). Directions for preparation and administration of the TPIP dose to the participant are provided in a separate document as an Appendix to the Pharmacy Manual.

All study IMP must be stored according to the labeled instructions in a secure cabinet or room with access restricted to necessary clinic personnel. The site will be required to keep a temperature log to establish a record of compliance with storage conditions. Current stability data supports a shelf life of 6 months for TPIP when stored at 2 to 8 °C.

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study IMP received and any discrepancies are reported and resolved before use of the study IMP.
- Only participants enrolled in the study may receive TPIP and only authorized site staff may supply or administer it. All TPIP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance

with the labeled storage conditions with access limited to the investigator and authorized site staff.

- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study IMP and dosing devices accountability, reconciliation, and record maintenance (eg, receipt, reconciliation, and final disposition records).
- Study IMP and dosing device accountability records will be maintained for all clinical supplies. All transactions will be recorded on the drug and dosing device accountability records including shipment receipts and study participant doses. All transactions will be recorded on a real-time basis.
- The Investigator/site will maintain detailed documentation of the number and identification of bottles and dispensing units of TPIP with copies of these documents to be provided to Insmed at the end of the study. All used and unused study IMP and dosing devices will be maintained by the site until inventoried by the study monitor. Upon completion of the study IMP and dosing device inventory by the study monitor, used and any unused study IMP and dosing devices will be disposed of in accordance with instructions provided to sites and according to site destruction policies. Documentation of destruction must be provided to Insmed.
- Further guidance and information for the final disposition of unused study IMP supplies can be obtained from Insmed.

6.3. Measures to Minimize Bias: Randomization and Blinding

Not applicable.

6.4. Study Intervention Compliance

Study participants will receive the TPIP dose directly from the investigator or designee, under medical supervision, in an appropriate inpatient setting. The date and time of the dose administered will be recorded in the source documents. The dose of TPIP and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the TPIP.

6.5. Dose Modification

Dose modification is part of the study design and is described in detail in Section 4.3.

6.6. Continued Access to Study Intervention After the End of the Study

Not applicable.

6.7. Treatment of Overdose

An overdose is defined as the participant receiving any TPIP in excess of their assigned dose as predetermined by the SRC (Section 4.3). An overdose itself is not an AE. However, if the overdose results in clinical signs and symptoms, it requires expedited reporting as if it is an SAE. The Investigators must refer to the relevant documents for detailed information regarding

warnings, precautions, contraindications, AEs, and other significant data pertaining to the study IMP. Such documents may include, but are not limited to, the Investigator's brochure.

In the event of an overdose, the investigator must:

- Contact the Medical Monitor within 24 hours.
- Evaluate the participant to determine, in consultation with the Medical Monitor, how to proceed with treatment period procedures and assessments.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until TP or TRE is likely to be sufficiently metabolized and/or excreted and/or can no longer be detected systemically. The frequency and duration of plasma sampling from the last dose of TPIP must be determined by the Investigator in conjunction with the study team and Medical Monitor.
- The overdose must be fully documented (eg, quantity of the excess dose, duration of the overdose, how it happened) in the CRF.

6.8. Concomitant Therapy

Any medications, treatments, or therapies that the participant is receiving at Baseline (Study Day 1) or receives during the study (Study Day 1 through Study Day 30) are considered concomitant therapy and will be collected and documented in the study CRF. Documentation includes the name of the therapy, with the reason for use, the dates of administration including start and end dates, and dosage information including dose and frequency.

Prior medications are those medications taken before the first dose of study IMP. A medication that starts prior to first dose but continues after the first dose of study IMP is classified both in prior and concomitant medications. Any procedures performed from Day 1 through Day 30 are considered concomitant procedures and will be collected and documented in the study CRF.

The Medical Monitor must be contacted if there are any questions regarding concomitant or prior therapy.

7. DISCONTINUATION OF STUDY IMP AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study IMP

This is a single dose study; not applicable

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.
- At the time of discontinuing from the study after TPIP administration, if possible, an early discontinuation evaluation must be conducted at the Investigator's discretion to maximize participant safety. This final evaluation and the reason for participant withdrawal must be documented in the CRF.
- If the participant is discontinued from the study due to an AE, the Investigator will follow the participant until the Investigator deems that the AE has resolved or stabilized. In case of unresolved AEs including significant abnormal laboratory values at the end of study assessment, these events will be followed up until resolution or until they become stable.
- The Investigator may withdraw the participant from the study due to absence of a PD response to TPIP. Lack of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the PK and PD assessments.
- The participant will be permanently discontinued both from the study IMP and from the study at that time.
- If the participant withdraws consent for disclosure of future information, Insmed may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled follow-up visits and is unable to be contacted by the study site.
The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts must be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered lost to follow-up and to have withdrawn from the study.

- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants, including those who did not get study IMP. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Insmed personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1.13.2).

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in Table 1, Table 2, Table 3, and Table 4.

All Screening evaluations must be completed and reviewed to confirm that potential participants meet eligibility criteria prior to scheduling the study RHC procedure and inpatient admission. The RHC procedure and inpatient admission must be scheduled for as soon as possible once the participant's eligibility for the study is confirmed by screening. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (e.g., previous RHC, previous echocardiogram, previous 6MWD test) and obtained before signing of the ICF may be utilized for Screening or Baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frames defined in the inclusion and exclusion criteria in Section 5

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required is expected to be approximately 150 mL and will not exceed 200 mL. Approximately 90 mL will be required for PK sampling over 48 hours and approximately 20 mL for biomarker sampling. Safety and Screening blood samples will require approximately 20 to 30 mL. Blood loss from the RHC procedure is anticipated to be negligible.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples at the Investigator's discretion.

At any time, the Investigator has the option to discontinue assessments for participant safety or tolerability reasons. Additional laboratory, PK, and/or hemodynamic assessments may be performed as deemed necessary for participant safety. Following completion of scheduled events, the investigator has the option of continued laboratory and/or hemodynamic monitoring as deemed appropriate for participant safety. If, in the interest of participant safety, the Investigator omits scheduled assessments/procedures or performs additional assessments/procedures, the reason for doing so must be reported on the CRF as an AE in order to avoid a protocol violation.

8.1. Pharmacodynamic Assessments

The results of each individual participant's PD assessments will contribute to the dosing decision for the next participant (Section 4.3).

8.1.1. Required PD Assessments With RHC

PVR, CO, PAP (mean), RAP (mean), RVP, hemoglobin, and MVO_2 will be measured via the RHC at the timepoints indicated in the SoA (Table 2). Oxygen consumption is part of the MVO_2 calculation and may be measured or estimated at 125 mL O_2 per square meter (m^2) of body surface area (BSA). These or other parameters may be optionally measured at other timepoints or omitted to ensure participant safety at the Investigator's discretion. If measurements are missed, or additional measurements are taken for safety purposes, the reason must be documented as an AE in the CRF.

Institutional procedures for insertion, care, monitoring, and removal of the RHC will be followed. Specific technique and procedures for measurement of PVR, CO, PAP, RAP, RVP, hemoglobin, oxygen consumption, and MVO_2 are provided in a separate Procedure Guide.

8.1.2. Required Non-invasive PD Assessments

Systemic blood pressure (mmHg) may be measured by inflatable cuff. Systemic blood pressure must include 3 values: systolic, diastolic, and mean arterial pressure. Arterial oxygen saturation (SpO_2, %) and heart rate (beats per minute) may be measured by pulse oximeter.

8.1.3. Resting Respiratory Gas Exchange Assessments

Specific measurements for resting respiratory gas exchange assessment include changes from Baseline in respiratory rate (breaths per minute), minute ventilation (mL per minute), carbon dioxide production (VCO_2, mL per minute), end tidal oxygen concentration (ETO_2, %), and end tidal carbon dioxide concentration ($ETCO_2$, %). The gas exchange parameters will be monitored at the same timepoints as the PD assessments in Section 8.1.1 (Table 2 Table 4). Specific instructions for resting respiratory gas exchange assessment procedures and measurements are provided in a separate Procedure Guide.

8.1.4. Transthoracic Echocardiogram Assessments

Transthoracic echocardiogram is to be performed at Baseline and during a 2-8 hour window following TPIP administration (Table 4). Specific instructions for echocardiographic procedures and measurements are provided in a separate Procedure Guide.

8.1.5. Pulmonary CT Scan

Pulmonary CT scanning to assess pulmonary vasculature and blood flow is scheduled for Baseline and during a 4-8 hour window following TPIP administration (Table 4). Specific requirements and instructions for pulmonary CT scanning and required parameters are provided in a separate Procedure Guide.

8.2. Safety Assessments

Evaluation of the safety and tolerability of single doses of TPIP in participants with PAH is the primary objective of this study. Planned time points for all safety assessments are provided in Table 1 and Table 2. The results of the individual participant's safety assessments during and after TPIP administration will contribute to the dosing decision for the next participant (Section 1.2.2).

8.2.1. Physical Examinations

Screening: The physical examination must focus on those areas that determine the individual participant's eligibility to participate in the study and do so safely at the Investigator's discretion and will be documented accordingly.

Baseline: The physical examination must focus on the participant's fitness for the study procedures and TPIP administration.

Discharge: The physical examination must focus on the participant's fitness to be safely discharged to home from the inpatient setting. Special attention must be paid to assessment of any new or ongoing AEs.

Follow-up: The in-person physical examination must focus on patient safety and assessment of AEs that were ongoing at discharge or have occurred since discharge.

8.2.2. Vital Signs

Temperature, heart rate, respiratory rate, and blood pressure at Screening and 48 hour post-TPIP administration follow-up will be per the Investigator's usual outpatient practice and documented accordingly.

Baseline and post-TPIP administration: Changes from Baseline in heart rate, respiratory rate, and systemic blood pressure are PD endpoints as well as safety variables and must be measured as specified (Section 8.1). Vital signs outside of PD endpoints will be monitored per the inpatient unit's usual practices.

8.2.3. Electrocardiograms

Screening: a single 12-lead ECG will be conducted per the Investigator's usual practice

Baseline: A single 12-lead ECG will be performed to ensure the participant's eligibility for the study (Section 5.2). Inpatient telemetry monitoring will be utilized per the unit's usual practice until the patient is discharged from the inpatient setting, but routine telemetry readings will not be collected as study data unless they pertain to a relevant AE.

48 hours post-TPIP administration follow-up: a single 12-lead ECG will be conducted per the Investigator's usual practice.

8.2.4. Clinical Safety Laboratory Assessments

See Section 10.2 (Table 5) for the list of clinical laboratory tests to be performed and to the SoA (Table 1, Table 2) for the timing and frequency. All clinical laboratory tests will be performed locally by the study site.

The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 7 days after TPIP dosing must be repeated at the Investigator's discretion, consistent with the participant's level of disease until the values return to normal or baseline or are no longer considered clinically significant by the investigator or Medical Monitor.

- If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology must be identified, and Insmed notified.]
- All protocol-required laboratory tests, as defined in Section 10, Appendix 2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).

- If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded.

8.2.5. Pregnancy Testing

Willingness of WOCBP to undergo serum or urine pregnancy testing is a study eligibility criterion. Pregnancy tests will be conducted at Screening, Baseline, and Study Day 30. WOCBP participants will be provided a home pregnancy test kit with instructions to conduct and report test results at the Study Day 30 follow-up visit which is scheduled to be by telephone call or telemedicine.

8.3. Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative). AEs may be solicited or unsolicited. Solicited and unsolicited AEs are defined in Section 10.3.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs will be collected from the signing of the ICF until the Study Day 30 follow-up visit at the time points specified in the SoA (Table 1, Table 2). Medical occurrences that begin after obtaining informed consent but before TPIP administration will be recorded as Medical History/Current Medical Conditions, not as AEs.

All SAEs will be collected from the signing of the ICF until the Study Day 30 follow-up visit at the time points specified in the SoA (Table 1, Table 2). SAEs that occur after signing the ICF but before study IMP starts must be recorded and reported as SAEs.

All SAEs will be recorded and reported to Insmed or designee immediately and under no circumstance must this exceed 24 hours, as indicated in Appendix 3, (Section 10.3). The investigator will submit any updated SAE data to Insmed within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study IMP or study participation, the investigator must promptly notify Insmed.

8.3.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AESIs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to Insmed of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Insmed has a legal responsibility to notify relevant health authorities and regulatory agencies about the safety of a study IMP under clinical investigation. This study is being conducted in the USA only; regulatory requirements relating to safety reporting to the US FDA, IRBs, and investigators will be followed.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from Insmed will review and then file it along with other study documents and will notify the IRB, if appropriate according to local requirements.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Insmed policy and forwarded to investigators as necessary. No serious adverse reactions are considered expected for TPIP. Please refer to the Reference Safety Information in Section 6.1 of the Investigators Brochure.

8.3.5. Pregnancy

Details of all pregnancies that occur in WOCBP participants within 30 days after TPIP administration will be collected. Male participants with WOCBP partners must continue to use contraception for 90 days after TPIP administration and report any pregnancies that occur within that time period.

If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to Insmed within 24 hours of learning of the pregnancy in a female participant or female partner of male participant and after obtaining the necessary signed informed consent from the female partner.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

The pregnant participant/pregnant female partner of a male participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the pregnant participant/pregnant female partner of a male participant and the neonate and the information will be forwarded to Insmed.

Any post-study pregnancy-related SAE considered reasonably related to the study IMP by the investigator will be reported to Insmed as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in pregnant former study participants or their pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study, prior to TPIP dosing will be discontinued from the study.

8.3.6. Cardiovascular and Death Events

Cardiovascular and death events must be reported as AEs/SAEs per the reporting instructions in Section 10.3.

8.3.7. Adverse Events of Special Interest (AESI)

AESIs are AEs related to prostacyclins, and prostacyclin analogs or receptor agonists. These include: headache, flushing, nausea, vomiting, diarrhea, cough, chest pain, abdominal pain/discomfort, jaw pain, back pain, extremity pain (musculoskeletal), and hypotension.

8.3.8. Medical Device Deficiencies

A medical device, the Plastiape capsule based Dry Powder Inhaler is being provided for use in this study to administer TPIP. To fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a Medical Device deficiency and reporting requirements and procedures for device deficiencies and AEs/SAEs resulting from device deficiencies can be found in Section 10.6.

8.3.8.1. Time Period for Detecting Medical Device Deficiencies

Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.

If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such a deficiency is considered reasonably related to a medical device provided for the study, the investigator will promptly notify Insmed.

The method of documenting Medical Device Deficiency is provided in Section 10.6.

8.3.8.2. Follow-Up of Medical Device Deficiencies

Follow-up applies to all participants who experienced a device deficiency.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.

New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

8.3.8.3. Prompt Reporting of Device Deficiencies to Insmed

Device deficiencies will be reported to Insmed within 24 hours after the investigator determines that the event meets the protocol definition of a medical device deficiency.

8.3.8.4. Regulatory Reporting Requirements for Device Deficiencies

The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for Insmed to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB.

8.4. Pharmacokinetic Assessments

The schedule for PK assessments and sampling windows is shown in Table 3. The 36 (± 3) and 48 (± 4) hour post-TPIP administration blood draws are expected to be done on an outpatient basis.

8.4.1. PK Sample Collection

Plasma blood samples of approximately 10 mL each will be collected for measurement of plasma concentrations of TP and TRE as specified in the SoA (Section 1.3).

A maximum of 2 samples may be collected at additional time points during the study if an SAE occurs or at early termination.

Each PK plasma sample will be divided into 2 aliquots (1 each for PK analysis and the other for backup. All samples will be stored frozen (-70°C or -20°C) until shipment and then stored at -70°C until analysis. The actual date and time (24-hour clock time) of each sample will be recorded.

Full instructions for the collection and handling of PK samples will be provided by Insmed in a separate Laboratory Manual.

8.4.2. PK Analysis

Individual PK parameters of TRE and TP will be determined using non-compartmental analysis for the following parameters: C_{max}, t_{max}, $AUC_{t1–t2}$, $AUC_{0–\infty}$, CL/F, Vd/F, and $t_{1/2.}$

8.4.3. Pharmacokinetic and Pharmacodynamic Evaluations

Relationships between PK (TP dose and TRE exposure) and PD effects and safety will be explored and reported separately.

8.5. Genetics / Pharmacogenomics

Genetic and/or pharmacogenomic analyses are not included in this study.

8.6. Biomarkers

A blood sample for NT-pro-BNP will be taken at Screening if needed as part of study inclusion criteria (Section 5.1).

Blood samples (5-7 mL per time point) will be collected for biomarker measurement at Baseline and at 4 and 8 hours after TPIP administration. The plasma generated from the blood samples will be stored frozen (-70 C or lower is preferred) until shipment and analysis.

Full instructions for the collection and handling of biomarker samples will be provided by Insmed in a separate Laboratory Manual.

8.7. Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

8.8. Immunogenicity Assessments

Immunogenicity assessments do not apply to this study of a small molecule.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

No statistical hypotheses will be evaluated in this study.

9.2. Sample Size Determination

The sample size for this study is not based on statistical power calculations. The planned number of evaluable participants to complete the study is approximately 6-10.

9.3. Analysis Sets

The analysis sets comprise participants who are considered evaluable for the parameters under consideration.

All participants who receive a single dose of TPIP will be considered evaluable for safety and included in the safety population.

All participants who receive a single dose of TPIP and have a least one measurable post-dose plasma TP/TRE concentration will be considered evaluable for PK and included in the PK population.

All participants who receive a single dose of TPIP and have a Baseline datapoint and at least one measurable post-dose PD datapoint will be considered evaluable for PD and included in the PD population.

All participants who receive a single dose of TPIP and have at least 1 measurable post-dose biomarker datapoint will be considered evaluable for biomarkers and included in the biomarker population.

9.4. Statistical Analyses

The statistical analysis plan will be finalized prior to Database Lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

There is no hypothesis-testing in this study and no inferential statistical analyses will be conducted. There will be no proxy values for missing data. Participant PK, PD, and biomarker data will be presented individually in listings and graphs as appropriate for each variable.

The frequency of TEAEs is the primary endpoint for this study. All safety analyses will be performed on the safety population. AE listings as required by ICH E3 guidelines will be produced. TEAEs, SAEs, AEs leading to treatment and/or study withdrawal, and AESIs will be listed for each participant along with outcome, severity, and relatedness to study IMP. Ad hoc summaries of TEAEs may be prepared if the volume of data allow.

PK and PD values for secondary endpoints will be listed and graphed if appropriate for each evaluable participant.

PK and PD values for exploratory endpoints will be listed and graphed as appropriate for each participant.

9.4.2. ECG, Vital Signs, Clinical Laboratory Values

ECG data will be listed for each participant. Vital signs data that are not considered part of a PD assessment (Section 8.1) will be listed for each participant. Clinical laboratory values will be listed for each participant.

9.5. Interim Analysis

All available safety, PK, and PD data from each participant will be evaluated by the SRC prior to the next participant in order to determine the value of proceeding with the study and the TPIP dose for each subsequent participant (Section 4.3).

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

a. Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
b. Applicable ICH Good Clinical Practice (GCP) Guidelines
c. Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, Instructions for Use of the Plastiape capsule based Dry Powder Inhaler, and other relevant documents must be submitted to an IRB by the investigator and reviewed and approved by the IRB before the study is initiated.

Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

d. Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
e. Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures
f. Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB, and all other applicable local regulations

10.1.2. Protocol Deviations

The Investigator must conduct the study in compliance with the protocol as agreed to by Insmed and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRB.

The Investigator must notify the IRB of deviations from the protocol in accordance with IRB reporting requirements.

As of May 2020, due to concern regarding COVID-19, there may be restrictions to participant attendance at in-clinic visits or elective inpatient admissions. In the event participants are restricted to attend in-clinic visits, or if the participant has concern regarding travel and attending in-clinic visits (due to potential public health concerns), the site must contact Insmed on how to conduct the scheduled assessments, and decisions must be documented in the source

documentation. Where necessary, in-clinic visits may be conducted via telemedicine link and home health care visits.

10.1.3. Public Health Emergency Situations

During the COVID-19 public health emergency, Insmed, IRBs, and Investigators shall follow the most current version of local guidance to assure the safety of study participants, maintain compliance with GCP, and minimize risks to study integrity. The continuity of clinical study conduct and oversight may require implementation of temporary or alternative mechanisms, which will remain in effect only for the duration of the local public health emergency. Examples of such mechanisms may include, but are not limited to, any of the following: telephone contact, virtual visits, telemedicine visits, online meetings, non-invasive remote monitoring devices, use of local clinic or laboratory locations, and home visits by skilled staff. The site must contact Insmed on how and when to implement temporary and/or alternative mechanism of scheduled assessments, and all decisions taken must be documented in the source documentation. Additionally, all temporary mechanisms utilized, and the resulting deviations from planned study procedures are to be documented as being related to COVID-19.

In a situation where local health authorities declare a public health emergency while the study is ongoing, the suggested guidance in the following subsections must be followed.

10.1.3.1. Continuation or Suspension of the Study

Ensuring the safety of trial participants is paramount. The Insmed (Insmed Incorporated), in consultation with clinical investigators and IRB, will determine if the protection of a participant's safety, welfare, and rights are best served by continuing or stopping the trial at the specific site. Such decision will depend on specific circumstances, including the ability to conduct appropriate safety monitoring, the potential impact on the investigational product supply chain, and other considerations.

If the decision is to continue the study, the following considerations will be taken into account:

10.1.3.1.1. Study Recruitment

The Insmed will communicate to the sites the decision on whether to continue or suspend recruitment after considering the specific circumstances of each site, recommendation by the IRB, and its local health authority mandates. If, due to COVID-19, study discontinuation exceeds the assumed rate, Insmed may allow enrollment past the assumed sample size.

10.1.3.1.2. Participants Already Enrolled in the Study

If the decision is to continue the participation of participants already enrolled, the following steps must be taken:

- If a participant is not able to complete a protocol specified study visit, it may be necessary to adjust the visit schedule, convert in-clinic visits to telemedicine visits, and/or postpone study procedures until the next available in-clinic study visit. If there is information available from previous visits (ie, laboratory assessments) that requires follow-up procedures or other safety assessments, the Investigator will decide if an

on-site visit or home healthcare visit is required or whether the participant's safety can be preserved by other means.

10.1.3.1.3. Participants Infected by COVID-19

If a participant has had a past documented mild to moderate COVID-19 infection prior to enrollment in the trial but the participant has recovered and the current diagnostic tests are negative (negative antigen by any diagnostic laboratory kit), the participant can be screened, at the Investigator's discretion. Participants who experienced hospitalization, severe disease, and/or COVID-19 acute respiratory distress syndrome (ARDS) must be excluded.

If a participant has a documented infection by COVID-19 while in the trial, the event will be reported as an AE or SAE, depending on the criteria. The Investigator will follow the guidance provided by health authorities in the treatment of those participants.

10.1.4. Financial Disclosure

The disclosed financial interest of the Investigator must be collected before Screening of the first participant, following study completion at the Investigator site and 1 year following overall study completion. The Investigator must promptly update this information if any relevant changes occur during this period.

10.1.5. Informed Consent Process

Before a participant's participation in the study, it is the Investigator's responsibility to obtain freely given consent, in writing, from the participant or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any study IMPs are administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective participant, to the participant's participation in the clinical study. An informed consent document that includes both information about the study and the consent form will be prepared and given to the participant. This document will contain all the elements required by the ICH E6 (R2) Guideline for GCP and any additional elements required by local regulations. The written ICF must be prepared in the local language(s) of the potential participant population.

In obtaining and documenting informed consent, the Investigator must comply with the applicable regulatory requirements, and must adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form and any revision(s) must be approved by the IRB prior to being provided to potential participants.

The participant's written informed consent (written or electronic) must be obtained prior to his/her participation in the study, and must be documented in the participant's medical records, as required by applicable regulations. The ICF must be signed and personally dated by the participant or a legally acceptable representative, and by the person who conducted the informed consent discussion (not necessarily the Investigator). The signed ICF must be retained in accordance with institutional policy, and a copy of the signed consent form must be provided to the participant or legal representative. The date and time that informed consent was given must be recorded in the CRF.

Participants who are rescreened are required to sign a new ICF.

10.1.6. Protection of Participant Identification and Confidentiality

The Investigators and Insmed will preserve the confidentiality of all participants taking part in the study, in accordance with GCP and local regulations.

The Investigator must ensure that the participant's anonymity is maintained. On the CRF or other documents submitted to Insmed, participants must be identified by a unique participant identifier as designated by Insmed. Documents that are not for submission to Insmed (eg, signed ICFs) must be kept in strict confidence by the Investigator.

In compliance with ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB direct access to review the participant's original medical records for verification of study-related procedures and data. The Investigator is obligated to inform the participant that his/her study-related records will be reviewed by the above-named representatives without violating the confidentiality of the participant.

Participant names will not be supplied to Insmed. A participant number will be recorded in the CRF, and if the participant name appears on any other document (eg, laboratory report), it must be obliterated on the copy of the document to be supplied to Insmed. All records will be kept confidential to the extent provided by federal, state, and local laws. The participants will be informed that representatives of Insmed, IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

The Investigator will maintain a personal participant identification list (participant numbers with the corresponding participant names) to enable records to be identified.

10.1.7. Committee Structure

A Safety Review Committee (SRC) will be chartered. The SRC will comprise all Investigators and key members of the Insmed Study Team (including but not limited to Medical Monitor, Medical Director(s), Safety/Pharmacovigilance Physician, Statistician, Clinical Pharmacologist) and possible external expert consultants. The SRC will continuously monitor all available safety, PD and PK data for each participant and will obtain consensus regarding the safety of continuing the study, the next TPIP dose, and clinical care of the next participant. Expert consultants may be invited to review and interpret participant data. With any safety findings, a decision will be made, based on the review, as to whether enrollment in the study will be allowed to continue. Decisions regarding final database values for PD parameters may adjudicated by the SRC.

10.1.8. Dissemination of Clinical Study Data

The Insmed will provide study information for inclusion in national registries according to national/local regulatory requirements.

Results of this study will be disclosed according to the relevant national regulatory requirements.

10.1.9. Data Quality Assurance

The Investigator/investigational site will permit study-related monitoring, audits, IRB review and regulatory inspections by providing direct access to source data/documents. Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of a clinical study.

10.1.9.1. Data Collection

All data obtained for this study will be entered into a 21 CFR Part 11 compliant Data Management System provided by Insmed or its designee. These data will be recorded with an EDC system using CRFs. The Investigator will ensure the accuracy and completeness of the data reported to Insmed. All data entry, modification or deletion will be recorded automatically in an electronic audit trail.

The Investigator will provide access to his/her original records to permit a representative from Insmed to verify the proper transcription of data. Data reported in the CRFs must be consistent with and substantiated by the participant's medical record and original source documents. The CRF data will be monitored by Insmed or designee. The final, completed CRF Casebook for each participant must be electronically signed and dated by the PI within the EDC system to signify that the Investigator has reviewed the CRF and certifies it to be complete and accurate.

The Insmed will retain the final CRF data and audit trail. A copy of all completed CRFs will be provided to the Investigator.

10.1.9.2. Study Monitoring

Before study initiation, at a site initiation visit or at an Investigator's meeting, a Insmed representative will review the protocol, CRF, Investigator Brochure, and any study related materials with the Investigators and their staff. During the study, the study Insmed monitor or its designee will visit the site regularly to check the completeness of participant records, the accuracy of entries on the CRFs, adherence to the protocol, adherence to ICH GCP and applicable regulatory requirements, the progress of enrollment, and also to ensure that study IMP is being stored, dispensed, and accounted for according to specifications.

The Investigator must give the monitor access to relevant hospital or clinical records to confirm their consistency with the CRF entries. Participant confidentiality will be maintained by the study center. The study Insmed monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of primary activity and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study specific monitoring plan.

10.1.9.3. Audits and Inspections

Domestic and foreign regulatory authorities, the IRB, and an auditor authorized by Insmed may request access to all source documents, CRFs, and other study documentation for onsite audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities. Medical records and other study documents may be copied during audit or inspection provided that participant names are obliterated on the copies to ensure confidentiality.

If an inspection is requested by a regulatory authority, the Investigator will inform the study Insmed, immediately that this request has been made.

10.1.9.4. Study Record Retention

Study documents must be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents must be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of Insmed. It is the responsibility of Insmed to inform the Investigator when these documents no longer need to be retained.

10.1.9.5. Source Documents

Source documentation is the point of initial recording of a piece of data. Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.10. Study Files and Materials

Before the start of any study related procedures, all initial documents required by ICH GCP, Good Pharmacoepidemiology Practice, and applicable local regulations must be available in the relevant files maintained by Insmed (or delegate) and the Investigator. An Investigator Study File prepared by Insmed (or delegate), containing all applicable documents for use at the study site, will be made available to the Investigator before the start of the study. A list of personnel and organizations responsible for conduct of the study as well as the list of Investigator-delegates (eg, sub-investigator) at each site will be included in the Investigator Study File. The respective files will be kept and updated by Insmed (or delegate) and the Investigator, as applicable.

All study documentation and materials maintained in the Investigator Study File at the study site must be available for inspection by Insmed's study monitor (or delegate) to determine that all required documentation is present and correct.

The study may be audited by qualified delegates from Insmed or a competent regulatory authority.

10.1.11. Use of Stored Samples and Data

Stored samples will be labeled with study and participant information and secured with limited access and retained per protocol requirements and in accordance with the laboratory's operating procedures. Electronic data will be kept in password protected computers at the laboratory and then transferred to Insmed or CRO, as applicable, for data analysis. Samples and corresponding data will be tracked using the laboratory's specimen tracking system.

Prior Insmed and IRB approval are required before using or sharing study samples or data in ways not specifically specified in the study protocol during conduct of this study.

Any loss or unanticipated destruction of samples (eg, freezer malfunction) or data (eg, loss of a data sheet with individually identifiable information) that violates or compromises the scientific integrity of study data must be reported to Insmed and the IRB.

At any time, participants may inform the Investigator in writing that they do not wish to have their samples stored beyond the completion (termination) of the study. In this case, the Investigator will request that all known remaining samples be destroyed and report the disposition of samples to the requesting participants and the IRB.

10.1.12. Disposition of Stored Samples and Data

Participant samples will be secured with limited access and retained per protocol requirements and in accordance with the laboratory's operating procedures. Samples stored by the central laboratories will be labeled with the participant's study identification information. Data will be kept in password protected computers at the laboratory and then transferred to the vendor for data analysis. Samples and corresponding data acquired will be tracked using the laboratory's specimen tracking system.

In the future, if other Investigators may wish to study these samples and/or data, they need to obtain Insmed approval and participant consent before any sharing of samples and/or data.

Any loss or unanticipated destruction of samples (eg, due to freezer malfunction) or data (eg, loss of a data sheet with individually identifiable information) that results in a violation that compromises the scientific integrity of the data collected for the study will be reported to Insmed and the IRB

Additionally, participants may withdraw authorization in writing to decline their sample storage for a period of up to 2 years beyond the duration of the study. In this case, the PI will request the destruction of all known remaining samples and report what was done to both the participant and to the IRB. This decision will not affect the individual's participation in the study.

10.1.13. Study and Site Start and Closure

Before the start of the study at each study site, Insmed's study monitor (or delegate) shall confirm adequacy of the facilities by study site visit or other acceptable methods.

The Investigator may not enroll any participant into the study before Insmed has received written approval or a favorable opinion from the IRB for conducting the study and a formal meeting has

been conducted by Insmed's study monitor (or delegate) to initiate the study. This meeting will include a detailed review of the study plan, and completion of the CRF.

10.1.13.1. First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants. The first patient screened for participation in the study is considered the first act of recruitment.

10.1.13.2. Study/Site Termination

The Insmed or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of Insmed. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.
The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.
Reasons for the early closure of a study site by Insmed or investigator may include but are not limited to:
For study termination:

- Discontinuation of further study IMP development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB or local health authorities, Insmed's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, Insmed shall promptly inform the investigators, the IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and must assure appropriate participant therapy and/or follow-up.

10.1.14. Protocol Amendments

Any substantial change or addition to this protocol requires a written protocol amendment that must be approved by Insmed, before implementation. Amendments significantly affecting the safety of participants, the scope of the investigation, or the scientific quality of the study, require additional approval by the applicable regulatory authority(ies) and IRBs. Copies of the applicable written approvals must be filed in Insmed files and investigator site files.

The requirements for approval must in no way prevent any immediate action from being taken by the Investigator or by Insmed in the interests of preserving the safety of all participants included in the study. If an immediate change to the protocol is felt to be necessary by the Investigator and is implemented by him/her for safety reasons, the study Insmed or its agent must be notified and the applicable regulatory authority(ies)/IRBs must be informed as soon as possible. Any other regional reporting requirements must be adhered to.

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or regulatory authority/IRB approval, but the regulatory authority(ies)/IRBs must

be kept informed of such administrative changes in accordance with country specific requirements.

10.1.15. Financing and Insurance

10.1.15.1. Finances

Prior to starting the study, the Investigator and/or institution will sign a clinical study agreement with Insmed. This agreement will include the financial information agreed upon by the parties.

10.1.15.2. Reimbursement, Indemnity, and Insurance

Reimbursement, indemnity, and insurance shall be addressed in a separate agreement on terms agreed upon by the parties.

10.1.15.3. Participant Reimbursement, Liability and Insurance

The civil liability of the involved parties with respect to financial loss due to personal injury and other damage that may arise as a result of this study being conducted are governed by the applicable legal requirement(s).

The Insmed will provide insurance to the Investigator if required by the applicable regulatory and legal requirement(s).

If required by local law, participants taking part in this study will be insured against any injury caused by the study in accordance with the applicable regulatory and legal requirement(s).

10.1.16. Publication Policy

Any formal presentation or publication of data collected from this study will be considered as a joint publication by the Investigator(s) and the appropriate personnel of the study Insmed. Authorship will be determined by mutual agreement. For multi-center studies, it is mandatory that the first publication be based on data from all centers, analyzed as stipulated in the protocol by the study Insmed and statisticians, and not by the Investigators themselves. Investigators participating in multi center studies agree not to present data gathered from a single center or a small group of centers before the full, initial publication, unless formally agreed to by all other Investigators and study Insmed.

The study Insmed must receive copies of any intended communication in advance of publication (at least 15 working days for an abstract or oral presentation and 45 working days for a journal submission). The study Insmed will review the communications for accuracy (thus avoiding potential discrepancies with submissions to regulatory authorities), verify that confidential information is not being inadvertently divulged, and to provide any relevant supplementary information. Authorship of communications arising from pooled data may include members from each of the contributing centers as well as the study Insmed personnel.

At the conclusion of the study, after the data are analyzed, the results of study will be reported in a clinical study report.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 5 will be performed by the local laboratory. If local laboratory results are used to make a study IMP decision or response evaluation, the results must be recorded. Protocol-specific clinical laboratory requirements for the inclusion or exclusion of participants are detailed in Section 5.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 5: Protocol-Required Safety Laboratory Tests, INS1009-201

Category	Laboratory Parameters
Clinical Chemistry	Sodium, chloride, potassium, CO_2, magnesium, calcium, glucose, phosphate, total bilirubin (with direct and indirect fractionation, if total bilirubin is elevated >2 ULN), alkaline phosphatase, LDH, AST, ALT, CPK, albumin, total protein, creatinine, urea-nitrogen, uric acid, estimated glomerular filtration rate
Hematology	Hemoglobin, erythrocytes, hematocrit, MCH, MCV, MCHC, leukocytes, differential blood count of neutrophils, eosinophils, basophils, monocytes, lymphocytes, and platelets
Coagulation	PT, PTT, INR
Serology	HIV antibody, hepatitis B surface antigen [HBsAg], Hepatitis C virus antibody
Pregnancy test	Highly sensitive serum or urine hCG

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CO_2 = carbon dioxide; CPK = creatine phosphokinase; hCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; INR = international normalized ratio; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PT = prothrombin time; PTT = partial thromboplastin time; ULN = upper limit of normal

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

The definitions and procedures in this Appendix (Appendix 3) are for AEs and SAEs that do not involve the Plastiape capsule based Dry Powder Inhaler. For reporting device deficiencies or AEs involving the Plastiape capsule based Dry Powder Inhaler, please see Section 10.6.

10.3.1. Definition of AE

AE Definition
An AE is defined as any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, October 1994). A treatment emergent adverse event (TEAE) is defined as any AE that occurs after the first dose of study IMP and within 28 days after the last dose of study IMP
Definition of Unsolicited and Solicited AE
An unsolicited adverse event is an adverse event that is communicated by a participant or their legal representative who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs. Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalisation, or emergency room visit, or visit to/by a health care provider). The participant or their legal representative will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records. Unsolicited AEs that are not medically attended nor perceived as a concern by the participant or their legal representative will be collected by interview with the participant/legal representative and by review of available medical records at the next visit. Solicited AEs are predefined local and systemic events for which the participant is specifically questioned and/or instructed to report.

Events Meeting the AE Definition
Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), that worsen from Baseline, are considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease), that are associated with signs and/or symptoms, require therapeutic intervention, or lead to discontinuation of the administration of study IMP must be reported as an AE

Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

New conditions detected or diagnosed after study IMP administration even though it may have been present before the start of the study.

Signs, symptoms, or the clinical sequelae of a suspected IMP- IMP interaction.

Signs, symptoms, or the clinical sequelae of a suspected overdose of either study IMP or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses must be reported regardless of sequelae.

The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. "Lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE. Lack of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the PK and PD assessments.

Events NOT Meeting the AE Definition

Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.

Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.

Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.

Study INS1009-201 requires an overnight inpatient treatment period (Study Days 1-2). Complications that occur during the inpatient treatment period are AEs. If a complication prolongs the planned hospitalization or fulfills any other serious criteria,

the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE must be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is a suspected transmission of any infectious agent via an authorized medicinal product

g. Is an important medical event

h. Other situations:

Medical or scientific judgment must be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events must usually be considered serious.

g. Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of IMP dependency or IMP abuse.

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant AE/SAE information.

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Insmed in lieu of completion of the completed AE reporting form.

There may be instances when copies of medical records for certain cases are requested by Insmed. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Insmed.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities.
Severe: An event that prevents normal everyday activities. An AE that is assessed as severe must not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

The investigator is obligated to assess the relationship between study IMP and each occurrence of each AE/SAE.
A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
The investigator will use clinical judgment to determine the relationship.
Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study IMP administration will be considered and investigated.
The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Insmed. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Insmed.
The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Insmed to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Insmed with a copy of any post-mortem findings including histopathology.
New or updated information will be recorded in the originally submitted documents.
The investigator will submit any updated SAE data to Insmed within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

All SAEs, regardless of causality, must be reported to the organization delegated by Insmed on a Serious Adverse Event Report Form within 24 hours of becoming aware of the event; corrections and additions are required to be submitted within 24 hours. Study-specific email, phone, and fax number for SAE reporting information will be provided to the study sites.

Unexpected drug related SAEs as assessed by Insmed or authorized person qualify for expedited reporting and will be reported to the IRB, regulatory authorities, participating Investigators and, if cross reporting is required for SUSARs, in accordance with all applicable global laws and regulations. A SUSAR is a Serious Adverse Reaction, which is suspected to be caused by the investigational medicinal product and which is unexpected, ie, its nature or severity is not consistent with the information in the relevant Reference Safety Information. SAEs, including those that do not meet requirements for expedited reporting, and all other AEs will be reported to the regulatory agencies as appropriate (ie, for the FDA these are reported in the Investigational New Drug annual report and for the European Medicines Agency, these are reported in the Development Safety Update Report).

SAE Reporting to Insmed via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Insmed will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Medical Monitor by telephone.

SAE Reporting to Insmed via Paper Data Collection Tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to Insmed.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting time frames.

10.4. Appendix 4: Contraceptive and Barrier Guidance

Contraceptive use by men and women of childbearing potential (WOCBP) must be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Highly effective contraception methods include true abstinence (refraining from heterosexual intercourse during the study); combined (estrogen and progestogen containing) or progestogen only hormonal contraception associated with inhibition of ovulation and supplemented with a double barrier (preferably male condom); intrauterine devices; intrauterine hormone-releasing systems; or vasectomized partner.

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

INTRODUCTION

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a participant meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with Insmed clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug-Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

DEFINITIONS

Potential Hy's Law (PHL)

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3×ULN and total bilirubin (TBL) ≥2×ULN at any point during the study irrespective of an increase in alkaline phosphatase (ALP). The elevations do not have to occur at the same time or within a specified time frame.

Hy's Law (HL)

AST or ALT ≥3× ULN and TBL ≥2×ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug. The elevations do not have to occur at the same time or within a specified time frame.

IDENTIFICATION OF POTENTIAL HY'S LAW CASES

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

1. ALT ≥ 3xULN
2. AST ≥ 3xULN
3. TBL ≥ 2xULN

The Investigator will review without delay each new laboratory report and if the identification criteria are met will:

1. Notify Insmed representative
2. Determine whether the participant meets PHL criteria (see DEFINITIONS of this Appendix) by reviewing laboratory reports from all previous visits
3. Promptly enter the laboratory data into the laboratory CRF

FOLLOW-UP

POTENTIAL HY'S LAW CRITERIA NOT MET

1. If the participant does not meet PHL criteria the Investigator will:
2. Inform Insmed representative that the participant has not met PHL criteria.
3. Perform follow-up on subsequent laboratory results according to the guidance provided in the clinical study protocol

POTENTIAL HY'S LAW CRITERIA MET

If the patient does meet PHL criteria the Investigator will:

- Notify Insmed representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or Baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician
- Complete the 3 Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

The instructions in this section must be followed for all cases where PHL criteria were met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than drug-induced liver injury caused by the IMP. The Insmed Medical Science Director and Global Safety Physician will also be involved in this review together with other participant matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

- If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE
- If the alternative explanation is not an AE, record the alternative explanation on the appropriate CRF

If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow Insmed standard processes.

If it is agreed that there is no explanation that would explain the ALT or AST and TBL elevations other than the IMP:

•Report an SAE (report term 'Hy's Law') according to Insmed standard processes.

- The ‘Medically Important’ serious criterion must be used if no other serious criteria apply
- As there is no alternative explanation for the HL case, a causality assessment of ‘related’ must be assigned.

If there is an unavoidable delay, of over 3 weeks in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term ‘Potential Hy’s Law’) applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

10.6. Appendix 6 Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

The definitions and procedures detailed in this appendix are in accordance with ISO 14155

Both the investigator and Insmed will comply with all local reporting requirements for medical devices.

The detection and documentation procedures described in this protocol apply to all Insmed medical devices provided for use in the study. See Section 6.1.1 for the list of Insmed medical devices.

10.6.1. Definition of Medical Device AE and ADE

Medical Device AE and ADE Definition
An AE is any untoward medical occurrence in a clinical study participant, users, or other persons, temporally associated with the use of study IMP, whether or not considered related to the investigational medical device. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved. An adverse device effect (ADE) is defined as an AE related to the use of an investigational medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.6.2. Definition of Medical Device SAE, SADE and USADE

A Medical Device SAE is an any serious adverse event that:
a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in: A life-threatening illness or injury. The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death if it were more severe. A permanent impairment of a body structure or a body function. Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function. Chronic disease (MDR 2017/745).
c. Led to fetal distress, fetal death, or a congenital abnormality or birth defect
d. Is a suspected transmission of any infectious agent via a medicinal product

SADE definition
A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of an SAE. Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.
Unanticipated SADE (USADE) definition
An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is defined as a serious adverse device effect that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report (Section 2.3).

10.6.3. Definition of Device Deficiency

Device Deficiency Definition
A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and information supplied by the manufacturer.

10.6.4. Recording and Follow-Up of AE and/or SAE and Device Deficiencies

AE, SAE, and Device Deficiency Recording
When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. The investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form. It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Insmed in lieu of completion of the AE/SAE/device deficiency form. There may be instances when copies of medical records for certain cases are requested by Insmed. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Insmed. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency. A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.
Assessment of Intensity
The investigator will make an assessment of intensity for each AE/SAE/device deficiency reported during the study and assign it to one of the following categories:

Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
Severe: An event that prevents normal everyday activities. An AE that is assessed as severe must not be confused with an SAE. "Severe" is a category used for rating the intensity of an event; both AEs and SAEs can be assessed as severe.
An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, **not** when it is rated as severe.

Assessment of Causality

The investigator is obligated to assess the relationship between study IMP and each occurrence of each AE/SAE/device deficiency.
A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship, cannot be ruled out.
The investigator will use clinical judgment to determine the relationship.
Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study IMP administration will be considered and investigated.
The investigator will also consult the Investigator's Brochure and/or Instructions for Use of the device in his/her assessment.
For each AE/SAE/device deficiency, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/device deficiency and has provided an assessment of causality.
There may be situations in which an SAE has occured and the investigator has minimal information to include in the initial report to Insmed. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Insmed.
The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE/SAE/device deficiency

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Insmed to elucidate the nature and/or causality of the AE/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Insmed with a copy of any post-mortem findings including histopathology.
New or updated information will be recorded in the originally completed form.

The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.6.5. Reporting of SAEs

SAE Reporting to Insmed via an Electronic Data Collection Tool

The primary mechanism for reporting an SAE to Insmed will be the electronic data collection tool.

If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next table) to report the event within 24 hours.

The site will enter the SAE data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next table) or to the Medical Monitor by telephone.

SAE Reporting to Insmed via Paper Data Collection Tool

Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to Insmed.

In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE paper data collection tool sent by overnight mail or courier service.

Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE paper data collection tool within the designated reporting time frames.

10.6.6. Reporting of SADEs

SADE Reporting to Insmed

NOTE: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

Any device deficiency that is associated with an SAE must be reported to Insmed within 24 hours after the investigator determines that the event meets the definition of a device deficiency.

The Insmed will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs as required by national regulations.

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